

-1-

BIOLOGICALLY ACTIVE COMPOUNDS

THIS INVENTION relates to compounds which are inhibitors across a broad range of cysteine proteases, to the use of these compounds, and to pharmaceutical compositions comprising them. Particular compounds of the invention are inhibitors of cathepsin K and related cysteine proteases of the CA clan. Furthermore, such compounds are useful for the *in vivo* therapeutic treatment of diseases in which participation of a cysteine protease is implicated.

Proteases form a substantial group of biological molecules which to date constitute approximately 2% of all the gene products identified following analysis of several completed genome sequencing programmes. Proteases have evolved to participate in an enormous range of biological processes, mediating their effect by cleavage of peptide amide bonds within the myriad of proteins found in nature. This hydrolytic action is performed by initially recognising, then binding to, particular three-dimensional electronic surfaces displayed by a protein, which aligns the bond for cleavage precisely within the protease catalytic site. Catalytic hydrolysis then commences through nucleophilic attack of the amide bond to be cleaved either *via* an amino acid side-chain of the protease itself, or through the action of a water molecule that is bound to and activated by the protease. Proteases in which the attacking nucleophile is the thiol side-chain of a Cys residue are known as cysteine proteases. The general classification of 'cysteine protease' contains many members found across a wide range of organisms from viruses, bacteria, protozoa, plants and fungi to mammals.

Cathepsin K and indeed many other crucial proteases belong to the papain-like CA C1 family. Cysteine proteases are classified into 'clans' based upon a similarity in the three-dimensional structure or a conserved arrangement of catalytic residues within the protease primary sequence. Additionally, 'clans' may be further classified into 'families' in which each protease shares a statistically significant relationship with other members when comparing the portions of amino acid sequence which constitute the parts responsible for the protease

-2-

activity (see Barrett, A.J *et al*, in 'Handbook of Proteolytic Enzymes', Eds. Barrett, A. J., Rawlings, N. D., and Woessner, J. F. Publ. Academic Press, 1998, for a thorough discussion).

5 To date, cysteine proteases have been classified into five clans, CA, CB, CC, CD and CE (Barrett, A. J. *et al*, 1998). A protease from the tropical papaya fruit 'papain' forms the foundation of clan CA, which currently contains over 80 distinct and complete entries in various sequence databases, with many more expected from the current genome sequencing efforts. Proteases of clan CA /
10 family C1 have been implicated in a multitude of house-keeping roles and disease processes. e.g. human proteases such as cathepsin K (osteoporosis), cathepsin S (autoimmune disorders), cathepsin L (metastases), cathepsin B (metastases, arthritis), cathepsin F (antigen processing), cathepsin V (T-cell selection), dipeptidyl peptidase I (granulocyte serine protease activation) or parasitic
15 proteases such as falcipain (malaria parasite *Plasmodium falciparum*) and cruzipain (*Trypanosoma cruzi* infection). Recently a bacterial protease, staphylopain (*S. aureus* infection) has also been tentatively assigned to clan CA. X-ray crystallographic structures are available for a range of the above mentioned proteases in complex with a range of inhibitors e.g. papain (PDB entries, 1pad,
20 1pe6, 1pip, 1pop, 4pad, 5pad, 6pad, 1ppp, 1the, 1csb, 1huc), cathepsin K (1au0, 1au2, 1au3, 1au4, 1atk, 1mem, 1bgo, 1ayw, 1ayu, 1nl6, 1nlj), cathepsin L (1cs8, 1mhw), cathepsin S (1glo, 1ms6 and currently on-hold but published McGrath, M. E. *et al*, *Protein Science*, 7, 1294-1302, 1998), cathepsin V (1fh0), dipeptidyl peptidase I (1jqp, 1k3b), cathepsin B (1gmy), cathepsin F (currently on-hold, but
25 published Somoza, J. R. *et al*, *J. Mol. Biol.*, 322, 559-568, 2002), cruzain (a recombinant form of cruzipain see Eakin, A. E. *et al*, 268(9), 6115-6118, 1993) (1ewp, 1aim, 2aim, 1F29, 1F2A, 1F2B, 1F2C), staphylopain (1cv8). Each of the structures displays a similar overall active-site topology, as would be expected by their 'clan' and 'family' classification and such structural similarity exemplifies
30 one aspect of the difficulties involved in discovering a selective inhibitor of cathepsin K suitable for human use. However, subtle differences in terms of the depth and intricate shape of the active site groove of each CA C1 protease are

-3-

evident, which may be exploited for selective inhibitor design. Additionally, many of the current substrate-based inhibitor complexes of CA C1 family proteases show a series of conserved hydrogen bonds between the inhibitor and the protease backbone, which contribute significantly to inhibitor potency. Primarily a bidentate hydrogen-bond is observed between the protease Gly66 (C=O)/ inhibitor N-H and the protease Gly66(NH)/inhibitor (C=O), where the inhibitor (C=O) and (NH) are provided by an amino acid residue NHCHRCO that constitutes the S2 sub-site binding element within the inhibitor (see Berger, A. and Schechter, I. *Philos. Trans. R. Soc. Lond. [Biol.]*, 257, 249-264, 1970 for a description of protease binding site nomenclature). A further hydrogen-bond between the protease main-chain (C=O) of asparagine or aspartic acid (158 to 163, residue number varies between proteases) and an inhibitor (N-H) is often observed, where the inhibitor (N-H) is provided by the S1 sub-site binding element within the inhibitor. Thus, the motif X-NHCHRCO-NH-Y is widely observed amongst the prior art substrate-based inhibitors of CA C1 proteases.

Cathepsin K is thought to be significant in diseases involving excessive loss of bone or cartilage. Bone consists of a protein matrix incorporating hydroxyapatite crystals. About 90% of the structural protein of the matrix is type I collagen, with the remainder comprising various non-collagenous proteins such as osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin and bone sialoprotein.

Skeletal bone is not a static structure but continually undergoes a cycle of bone resorption and replacement. Bone resorption is carried out by osteoclasts, which are multinuclear cells of haematopoietic lineage. Osteoclasts adhere to the bone surface and form a tight sealing zone. The membrane on the apical surface of the osteoclasts is folded so as to create a closed extracellular compartment between the osteoclast and the bone surface, which is acidified by proton pumps in the osteoclast membrane. Proteolytic enzymes are secreted into the compartment from the osteoclast. The high acidity in the compartment causes the hydroxyapatite at the surface of the bone to be dissolved and the proteolytic

-4-

enzymes break down the protein matrix causing a resorption lacuna to be formed. Following bone resorption, osteoblasts produce a new protein matrix that is subsequently mineralised.

- 5 In disease states such as osteoporosis and Paget's disease, the bone resorption and replacement cycle is disrupted leading to a net loss of bone with each cycle. This leads to weakening of the bone and therefore to increased risk of bone fracture.

- 10 Cathepsin K is expressed at a high level in osteoclasts and is therefore thought to be essential for bone resorption. Therefore, selective inhibition of cathepsin K is likely to be effective in the treatment of diseases involving excessive bone loss. These include osteoporosis, gingival diseases such as gingivitis and periodontitis, Paget's disease, hypercalcaemia of malignancy and metabolic bone disease.

- 15 In addition to osteoclasts, high levels of cathepsin K are also found in chondroclasts from the synovium of osteoarthritic patients. It therefore appears that cathepsin K inhibitors will be of use in the treatment of diseases involving matrix or cartilage degradation, in particular osteoarthritis and rheumatoid arthritis.

- 20 Elevated levels of cathepsin K are also found in metastatic neoplastic cells which suggests that cathepsin K inhibitors may also be useful for treating certain neoplastic diseases.

- 25 In the prior art, the development of cysteine protease inhibitors for human use has recently been an area of intense activity (*e.g.* see Bromme, D. and Kaleta, J., *Curr. Pharm. Des.*, 8, 1639-1658, 2002; Kim, W. and Kang, K., *Expert Opin. Ther. Patents*, 12(3), 419-432, 2002; Leung-Toung, R. *et al.* *Curr. Med. Chem.*, 9, 979-1002, 2002; Lecaille, F. *et al.*, *Chem. Rev.*, 102, 4459-4488, 2002; Hernandez, A. A. and Roush, W. R., *Curr. Opin. Chem. Biol.*, 6, 459-465, 2002). Considering the
30 CA C1 family members, particular emphasis has been placed upon the development of inhibitors of human cathepsins, primarily cathepsin K

-5-

(osteoporosis), cathepsin S (autoimmune disorders), cathepsin L (metastases), cathepsin B (metastases, arthritis), cathepsin F (antigen processing), cathepsin V (T-cell selection) and dipeptidyl peptidase I (granulocyte serine protease activation), through the use of peptide and peptidomimetic nitriles (e.g. see WO-A-03041649, WO-A-03037892, WO-A-03029200, WO-A-02051983, WO-A-02020485, US-A-20020086996, WO-A-01096285, WO-A-0109910, WO-A-0051998, WO-A-0119816, WO-A-9924460, WO-A-0049008, WO-A-0048992, WO-A-0049007, WO-A-0130772, WO-A-0055125, WO-A-0055126, WO-A-0119808, WO-A-0149288, WO-A-0147886), linear and cyclic peptide and peptidomimetic ketones (e.g. see Veber, D. F. and Thompson, S. K., *Curr. Opin. Drug Discovery Dev.*, 3(4), 362-369, 2000, WO-A-02092563, WO-A-02017924, WO-A-01095911, WO-A-0170232, WO-A-0178734, WO-A-0009653, WO-A-0069855, WO-A-0029408, WO-A-0134153 to WO-A-0134160, WO-A-0029408, WO-A-9964399, WO-A-9805336, WO-A-9850533), ketoheterocycles (e.g. see WO-A-02080920, WO-A-03042197, WO-A- WO-A-03024924, WO-A-0055144, WO-A-0055124), monobactams (e.g. see WO-A-0059881, WO-A-9948911, WO-A-0109169), α -ketoamides (e.g. see WO-A-03013518), cyanoamides (WO-A-01077073, WO-A-01068645), dihydro pyrimidines (e.g. see WO-A-02032879) and cyanoaminopyrimidines (e.g. see WO-A-03020278, WO-A-03020721). The prior art describes potent *in vitro* inhibitors, but also highlights the many difficulties in developing a human therapeutic. For example, WO-A-9850533 and WO-A-0029408 describe compounds that may be referred to as cyclic ketones and are inhibitors of cysteine proteases with a particular reference towards papain family proteases and as a most preferred embodiment, cathepsin K. WO-A-9850533 describes compounds subsequently detailed in the literature as potent inhibitors of cathepsin K with good oral bioavailability (Witherington, J., 'Tetrahydrofurans as Selective Cathepsin K Inhibitors', RSC meeting, Burlington House, London, 1999). The compounds of WO-A-9850533 were reported to bind to cathepsin K through the formation of a reversible covalent bond between the tetrahydrofuran carbonyl and the active site catalytic cysteine residue (Witherington, J., 1999). Additionally, the same cyclic ketone compounds are described in WO-A-9953039 as part of a wide-ranging description of inhibitors of

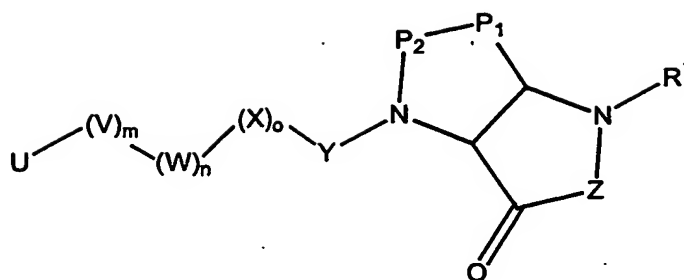
cysteine proteases associated with parasitic diseases, with particular reference to the treatment of malaria by inhibition of falcipain. However, subsequent literature describes the cyclic ketone compounds of WO-A-9850533 to be unsuitable for further development or for full pharmacokinetic evaluation due to a physiochemical property of the inhibitors, the poor chiral stability of the α -aminoketone chiral centre (Marquis, R. W. *et al*, J. Med. Chem., 44(5), 725-736, 2001). WO-A-0069855 describes compounds that may also be referred to as cyclic ketones with particular reference towards inhibition of cathepsin S. The compounds of WO-A-0069855 are considered to be an advance on compounds of WO-A-9850533 due to the presence of the β -substituent on the cyclic ketone ring system that provides chiral stability to the α -carbon of the cyclic ketone ring system. However, the compounds of WO-A-0069855 and indeed those of WO-A-9850533 describe a requirement for the presence of the potential hydrogen-bonding motif X-NHCHRCO-NH-Y that is widely observed amongst the prior art substrate-based inhibitors of CA C1 proteases.

Our earlier patent application (WO-A-02057270) describes bicyclic compounds in which the chirality of the α -aminoketone is stabilised (for a review of energetic considerations within fused ring systems see Toromanoff, E. *Tetrahedron Report No 96*, 36, 2809-2931, 1980). These compounds do not contain the X-NHCHRCO-NH-Y motif and yet the compounds are highly potent inhibitors across a broad range of CA C1 cysteine proteases. In particular, certain of the compounds are potent and selective cruzipain inhibitors.

The present invention relates to variants of the compounds described in WO-A-02057270 which are also inhibitors of a wide range of CA C1 cysteine protease. In particular, some compounds of the present invention are potent and selective inhibitors of cathepsin K.

Therefore, in the present invention, there is provided a compound of general formula (I)

-7-



(I)

wherein:

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$Z = CR^3R^4$, where R^3 and R^4 are independently chosen from C_{0-7} -alkyl (when $C = 0$, R^3 or R^4 is simply a hydrogen atom), C_{3-6} -cycloalkyl, $Ar-C_{0-7}$ -alkyl (when $C = 0$, R^3 or R^4 is simply an aromatic moiety Ar),

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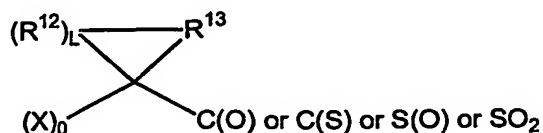
$P_1 = CR^5R^6$, where R^5 and R^6 are independently chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl, $Ar-C_{0-7}$ -alkyl, $O-C_{0-7}$ -alkyl, $O-C_{3-6}$ -cycloalkyl, $O-Ar-C_{0-7}$ -alkyl, $S-C_{0-7}$ -alkyl, $S-C_{3-6}$ -cycloalkyl, $S-Ar-C_{0-7}$ -alkyl, $NH-C_{0-7}$ -alkyl, $NH-C_{3-6}$ -cycloalkyl, $NH-Ar-C_{0-7}$ -alkyl, $N(C_{0-7}\text{-alkyl})_2$, $N(C_{3-6}\text{-cycloalkyl})_2$ or $N(Ar-C_{0-7}\text{-alkyl})_2$;

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$P_2 = O$, CR^7R^8 or NR^9 , where R^7 and R^8 are independently chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl, $Ar-C_{0-7}$ -alkyl and R^9 is chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl or $Ar-C_{0-7}$ -alkyl;

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$Y = CR^{10}R^{11}-C(O)$ or $CR^{10}R^{11}-C(S)$ or $CR^{10}R^{11}-S(O)$ or $CR^{10}R^{11}-SO_2$ where R^{10} and R^{11} are independently chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl and $Ar-C_{0-7}$ -alkyl, or Y represents



where L is a number from one to four and R^{12} and R^{13} are independently chosen from $CR^{14}R^{15}$ where R^{14} and R^{15} are independently chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl, Ar- C_{0-7} -alkyl or halogen; and for each R^{12} and R^{13} either R^{14} or R^{15} (but not both R^{14} and R^{15}) may additionally be chosen from O- C_{0-7} -alkyl, O- C_{3-6} -cycloalkyl, O-Ar- C_{0-7} -alkyl, S- C_{0-7} -alkyl, S- C_{3-6} -cycloalkyl, S-Ar- C_{0-7} -alkyl, NH- C_{0-7} -alkyl, NH- C_{3-6} -cycloalkyl, NH-Ar- C_{0-7} -alkyl, N-(C_{0-7} -alkyl)₂, N-(C_{3-6} -cycloalkyl)₂, and N-(Ar- C_{0-7} -alkyl)₂;

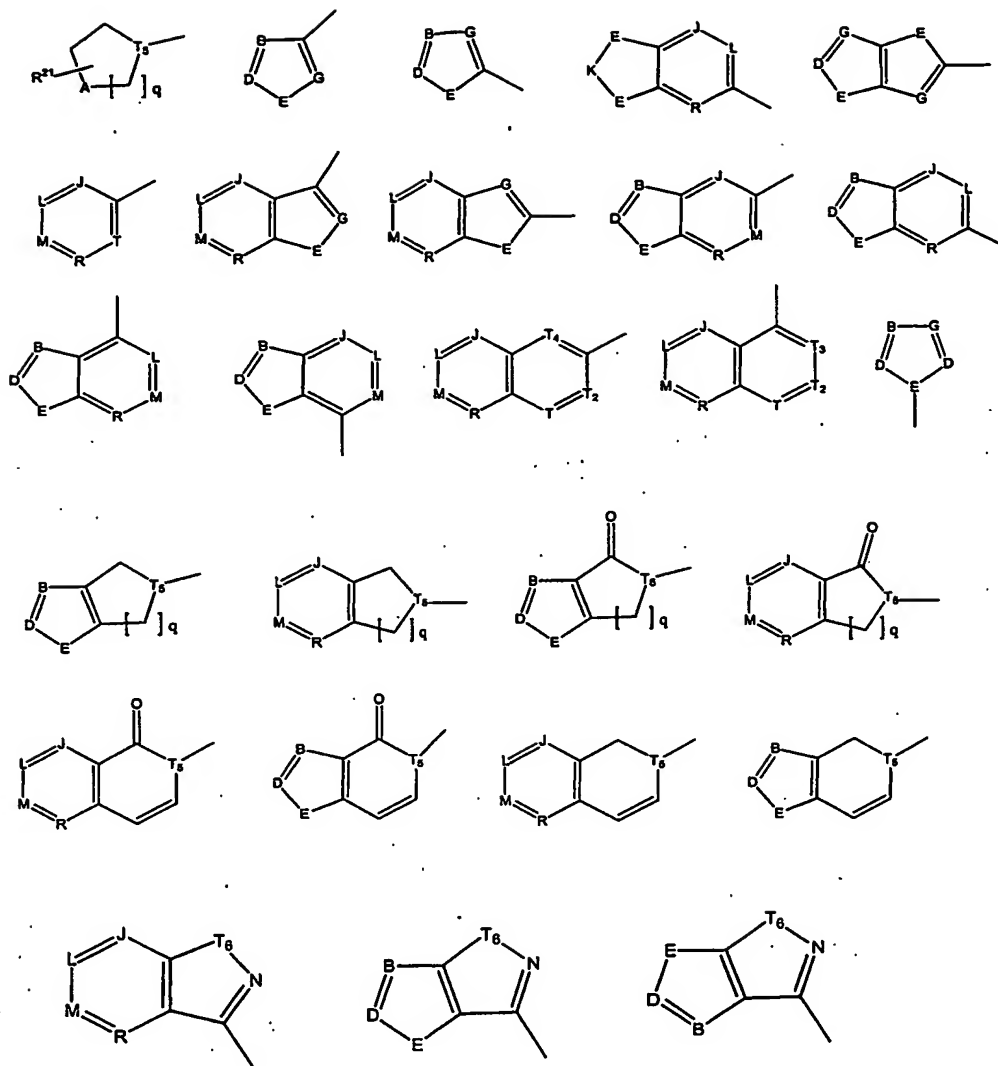
$(X)_o = CR^{16}R^{17}$, where R^{16} and R^{17} are independently chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl and Ar- C_{0-7} -alkyl and o is a number from zero to three;

$(W)_n = O, S, C(O), S(O)$ or $S(O)_2$ or NR^{18} , where R^{18} is chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl and Ar- C_{0-7} -alkyl and n is zero or one;

$(V)_m = C(O), C(S), S(O), S(O)_2, S(O)_2NH, OC(O), NHC(O), NHS(O), NHS(O)_2, OC(O)NH, C(O)NH$ or $CR^{19}R^{20}, C=N-C(O)-OR^{19}$ or $C=N-C(O)-NHR^{19}$, where R^{19} and R^{20} are independently chosen from C_{0-7} -alkyl, C_{3-6} -cycloalkyl, Ar- C_{0-7} -alkyl and m is a number from zero to three, provided that when m is greater than one, $(V)_m$ contains a maximum of one carbonyl or sulphonyl group;

U = a stable 5- to 7-membered monocyclic or a stable 8- to 11-membered bicyclic ring which is either saturated or unsaturated and which includes zero to four heteroatoms (as detailed below):

-9-



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wherein R^{21} is:

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C_{0-7} -alkyl, C_{3-6} -cycloalkyl, Ar- C_{0-7} -alkyl, O- C_{0-7} -alkyl, O- C_{3-6} -cycloalkyl, O-Ar- C_{0-7} -alkyl, S- C_{0-7} -alkyl, S- C_{3-6} -cycloalkyl, S-Ar- C_{0-7} -alkyl, SO_2 - C_{0-7} -alkyl, SO_2 - C_{3-6} -cycloalkyl, SO_2 -Ar- C_{0-7} -alkyl, NH- C_{0-7} -alkyl, NH- C_{3-6} -cycloalkyl, NH-Ar- C_{0-7} -alkyl, $N(C_{0-7}\text{-alkyl})_2$, $N(C_{3-6}\text{-cycloalkyl})_2$ or $N(\text{Ar-}C_{0-7}\text{-alkyl})_2$; or, when part of a CHR^{21} or CR^{21} group, R^{21} may be halogen;

-10-

A is chosen from:

CH_2 , CHR^{21} , O, S, SO_2 , NR^{22} or N-oxide ($\text{N}\rightarrow\text{O}$), where
 R^{21} is as defined above; and R^{22} is chosen from C_{0-7} -alkyl,
 C_{3-6} -cycloalkyl and Ar- C_{0-7} -alkyl;

B, D and G are independently chosen from:

CR^{21} , where R^{21} is as defined above, or N or N-oxide
($\text{N}\rightarrow\text{O}$);

E is chosen from:

CH_2 , CHR^{21} , O, S, SO_2 , NR^{22} or N-oxide ($\text{N}\rightarrow\text{O}$), where
 R^{21} and R^{22} are defined as above;

K is chosen from:

CH_2 , CHR^{22} , where R^{22} is defined as above;

J, L, M, R, T, T_2 , T_3 and T_4 are independently chosen from:

CR^{21} where R^{21} is as defined above, or N or N-oxide
($\text{N}\rightarrow\text{O}$);

T_5 is chosen from:

CH or N;

T_6 is chosen from:

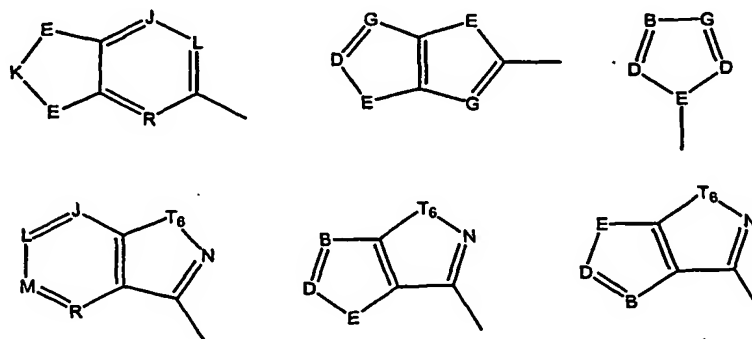
NR^{22} , SO_2 , $\text{OC}(\text{O})$, $\text{C}(\text{O})$, $\text{NR}^{22}\text{C}(\text{O})$;

q is a number from one to three, thereby defining a 5-, 6- or 7-membered
ring;

-11-

$R^1 = R^2C(O), R^2OC(O), R^2NQC(O), R^2SO_2$, where R^2 is chosen from C_{1-7} -alkyl, C_{3-6} -cycloalkyl or Ar- C_{0-7} -alkyl (when $C = 0$, R^2 is simply an aromatic moiety Ar) and Q is C_{0-7} -alkyl;

5 provided that when Y is other than $CR^{10}R^{11}-C(O)$ or when U is:



R^1 may also be C_{0-7} -alkyl, C_{3-6} -cycloalkyl or Ar- C_{0-7} -alkyl.

10 The present invention includes all salts, hydrates, solvates, complexes and prodrugs of the compounds of this invention. The term "compound" is intended to include all such salts, hydrates, solvates, complexes and prodrugs, unless the context requires otherwise.

15 Appropriate pharmaceutically and veterinarily acceptable salts of the compounds of general formula (I) include salts of organic acids, especially carboxylic acids, including but not limited to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate, pantothenate, adipate, alginate, aspartate, benzoate, butyrate, digluconate, cyclopentanoate, glucoheptanoate, glycerophosphate, oxalate, heptanoate, hexanoate, fumarate, nicotinate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, propionate, tartrate, lactobionate, pivalate, camphorate, undecanoate and succinate, organic sulphonic acids such as
20 methanesulphonate, ethanesulphonate, 2-hydroxyethane sulphonate, camphorsulphonate, 2-naphthalenesulphonate, benzenesulphonate, p-chlorobenzenesulphonate and p-toluenesulphonate; and inorganic acids such as
25 hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, hemisulphate,

-12-

thiocyanate, persulphate, phosphoric and sulphonic acids. Salts which are not pharmaceutically or veterinarily acceptable may still be valuable as intermediates.

Prodrugs are any covalently bonded compounds which release the active parent drug according to general formula (I) *in vivo*. A prodrug may for example constitute an acetal or hemiacetal derivative of the exocyclic ketone functionality present in the hexahydropyrrolo[3,2-*b*]pyrrol-3-one, hexahydropyrrolo[3,2-*c*]pyrazol-6-one or hexahydro-2-oxa-1,4-diazapentalen-6-one scaffold. If a chiral centre or another form of isomeric centre is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereoisomers, are intended to be covered herein. Compounds of the invention containing a chiral centre may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone.

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'Halogen' as applied herein is meant to include F, Cl, Br, I;

'Heteroatom' as applied herein is meant to include O, S and N;

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'C₀₋₇-alkyl' as applied herein is meant to include stable straight and branched chain aliphatic carbon chains containing zero (*i.e.* simply hydrogen) to seven carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, heptyl and any simple isomers thereof. Additionally, where 'C₀₋₇-alkyl' contains 2 or more contiguous carbon atoms, an alkene (-CH=CH-) may be present. Additionally, any C₀₋₇-alkyl may optionally be substituted at any point by one, two or three halogen atoms (as defined above) for example to give a trifluoromethyl substituent. Furthermore, C₀₋₇-alkyl may contain one or more heteroatoms (as defined above) for example to give ethers, thioethers, sulphones, sulphonamides, substituted amines, amidines, guanidines, carboxylic acids, carboxamides. If the heteroatom is located at a chain terminus then it is appropriately substituted with one or two hydrogen atoms. A heteroatom or halogen is only present when C₀₋₇-alkyl contains a minimum of one carbon

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-13-

atom. For example, the group $\text{CH}_3\text{-CH}_2\text{-O-CH}_2\text{-CH}_2\text{-}$ is defined within 'C₀₋₇-alkyl' as a C₄ alkyl that contains a centrally positioned heteroatom whereas the group $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-}$ is defined within 'C₀₋₇-alkyl' as an unsubstituted C₄ alkyl.

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'C₃₋₆-cycloalkyl' as applied herein is meant to include any variation of 'C₀₋₇-alkyl' which additionally contains a carbocyclic ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. The carbocyclic ring may optionally be substituted at any position with one or more halogens (as defined above) or heteroatoms (as defined above) for example to give a tetrahydrofuran, pyrrolidine, piperidine, piperazine or morpholine substituent.

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'Ar-C₀₋₇-alkyl' as applied herein is meant to include any variation of C₀₋₇-alkyl which additionally contains an aromatic ring moiety 'Ar'. The aromatic ring moiety Ar can be a stable 5 or 6-membered monocyclic or a stable 8 to 10 membered bicyclic ring which is unsaturated, as defined previously for U in general formula (I). The aromatic ring moiety Ar may be substituted by R²¹ (as defined above for U in general formula (I)). When C = 0 in the substituent Ar-C₀₋₇-alkyl, the substituent is simply the aromatic ring moiety Ar.

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Other expressions containing terms such as alkyl and cycloalkyl are intended to be construed according to the definitions above. For example "C₁₋₄ alkyl" is the same as C₀₋₇-alkyl except that it contains from one to four carbon atoms.

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If different structural isomers are present, and/or one or more chiral centres are present, all isomeric forms are intended to be covered. Enantiomers are characterised by the absolute configuration of their chiral centres and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Such conventions are well known in the art (e.g. see 'Advanced Organic Chemistry', 3rd edition, ed. March, J., John Wiley and Sons, New York, 1985). It is also intended to include compounds of general formula (I) where any hydrogen atom has been replaced by a deuterium atom.

-14-

Compounds of general formula I are inhibitors of a wide range of CA C1 cysteinyl proteases for example cathepsin K, cathepsin S, cathepsin L, cathepsin F, cathepsin B, cruzipains, falcipains and *leishmania mexicana* CPB protease.

5 For all the above mentioned CA C1 proteases, the preferred fundamental backbone shape of inhibitor molecules is broadly similar. Therefore, the preferred compounds of general formula (I) will have similar (V)_m, (W)_n, (X)_o and R¹ whether they act as cathepsin K cathepsin S, cathepsin L, cathepsin F, cathepsin B, cruzipains, falcipains or *leishmania mexicana* CPB protease inhibitors. Within
10 general formula (I), inhibitory potency and selectivity for each CA C1 protease is primarily determined by different preferences for the Y and U groups for each CA C1 protease.

Preferred compounds of general formula (I) include, but are not limited to those
15 which, independently or in any combination:

Z is CH₂;

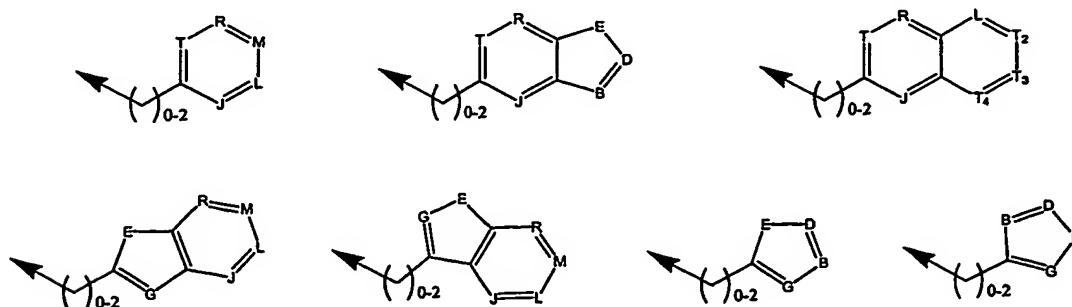
P¹ is CH₂;

P² is CH₂, O or NH.

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As mentioned above, cysteine protease inhibitors of general formula (I), comprise an R² group chosen from C₁₋₇-alkyl, C₃₋₆-cycloalkyl and Ar-C₀₋₇-alkyl.

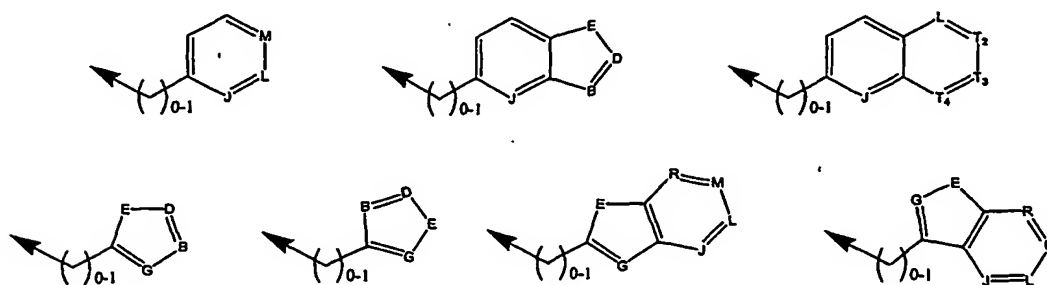
When R² comprises Ar-C₀₋₇-alkyl, preferred R² groups comprise Ar-C₀₋₂-alkyl and
25 examples include but are not limited to:



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where J, L, M, R, T, T₂, T₃ and T₄, B, D, G and E are as previously defined.

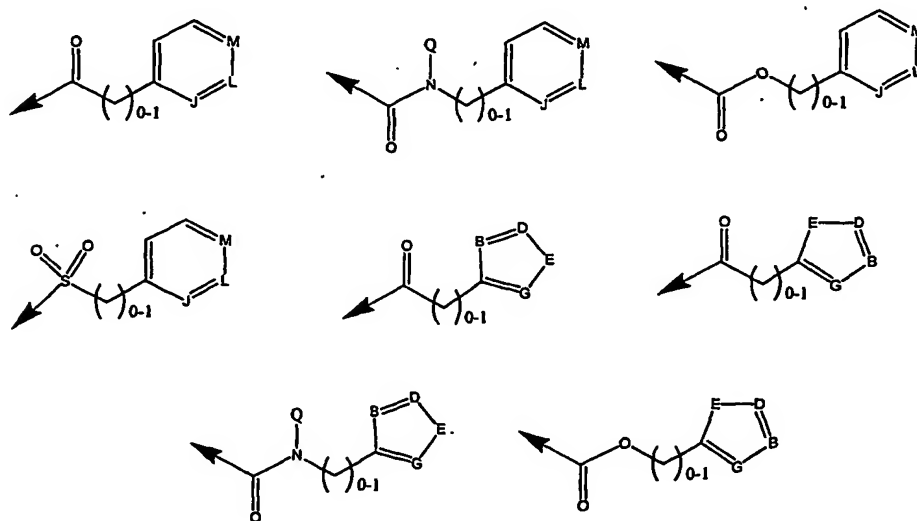
- 5 More preferred R² comprises Ar-C₀₋₁-alkyl and examples of such R² groups include, but are not limited to:



where J, L, M, T₂, T₃, T₄, B, D, G and E are as previously defined.

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Still more active compounds of general formula (I) are those in which R² comprises a monocyclic Ar-C₀₋₁-alkyl and forms part of an R¹ group such as:



wherein:

-16-

J, L, M, B, D and G are as defined above (i.e. CR^{21} , N or $N \rightarrow O$) and wherein R^{21} is chosen from hydrogen, methyl, methoxy, ethyl, isopropyl, trifluoromethyl, trifluoromethoxy, F, Cl, SO_2Me ; and

E is as previously defined; and

5 Q is chosen from hydrogen or methyl.

In cysteine protease inhibitors of general formula (I) when R^2 is C_{1-7} -alkyl, preferred R^2 groups comprise C_{3-7} -alkyl which may include an -O- or -NH- as part of the chain and which is either unsubstituted or is substituted with one or more
10 NH_2 , $NHMe$, $NHC(O)CH_3$, $NMeC(O)CH_3$, OH or OMe groups.

When R^2 is C_{3-7} -alkyl, more preferred groups include C_{3-6} -alkyl, in particular those which are branched at the α -position or which include an NH_2 , $NHMe$, $NHC(O)CH_3$, $NMeC(O)CH_3$, OH or OMe substituent at the α -position.

15

In cysteine protease inhibitors of general formula (I) when R^2 is C_{3-6} -cycloalkyl, R^2 may include a heteroatom in the ring system. Examples of R^2 groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolidine, piperidine, morpholine, tetrahydrofuran, cyclopentene, cyclopentadiene, cyclohexadiene and
20 piperazine. Nitrogen-containing rings may be N-substituted with groups such as C_{1-4} alkyl, phenyl or benzyl.

It is yet more preferred that when R^2 is a C_{3-6} -cycloalkyl group, the ring system is either connected directly to the remainder of the R^1 moiety or there is one
25 intervening methylene group. The inventors have found that the activity of the molecule increases with the size of the cycloalkyl ring and therefore compounds in which R^2 is a five- or six-membered cyclic ring are most favourable.

In compounds of general formula (I), particularly preferred R^1 groups therefore
30 include:

-17-

benzoyl; pyridine-2-carbonyl; 1-oxy-pyridine-2-carbonyl; pyridine-3-carbonyl; 1-oxy-pyridine-3-carbonyl; pyridine-4-carbonyl; 1-oxy-pyridine-4-carbonyl; phenylsulphonyl; pyridine-2-sulphonyl; 1-oxy-pyridine-2-sulphonyl; pyridine-3-sulphonyl; 1-oxy-pyridine-3-sulphonyl; pyridine-4-sulphonyl; 1-oxy-pyridine-4-sulphonyl; 5
sulphonyl; phenylacetyl; phenylcarbamoyl; isobutylcarbamoyl; phenyloxycarbonyl; isobutyloxycarbonyl; pyrrolidine-N-carbonyl; piperidine-N-carbonyl; morpholine-N-carbonyl; piperazine-N-carbonyl; 4-methyl-piperazine-N-carbonyl; (4-methyl-piperazin-1-yl)-acetyl; piperazin-1-yl-acetyl; furan-2-carbonyl; 5-chlorofuran-2-carbonyl; thiophene-2-carbonyl; 5-chlorothiophene-2-carbonyl; furan-3-carbonyl; thiophene-3-carbonyl; cyclopentoyl; cyclohexoyl; 10
cyclopent-3-enoyl; cyclopentylmethylcarbonyl; cyclohexylmethylcarbonyl; pyrrolidine-2-carbonyl; N-acetyl-pyrrolidine-2-carbonyl; piperidine-2-carbonyl; N-acetyl-piperidine-2-carbonyl; tetrahydrofuran-2-carbonyl; 1-aminocyclobutanoyl; 1-aminocyclopentanoyl; 1-aminocyclohexanoyl; N-acetyl-1-aminocyclobutanoyl; N-acetyl-1-aminocyclopentanoyl; N-acetyl-1-aminocyclohexanoyl; 1-hydroxycyclobutanoyl; 1-hydroxycyclopentanoyl; 1-hydroxycyclohexanoyl; 1-methoxycyclobutanoyl; 1-methoxycyclopentanoyl; 1-methoxycyclohexanoyl; aminocyclopentylacetyl; aminocyclohexylacetyl; N-acetylaminocyclopentylacetyl; N-acetylaminocyclohexylacetyl; 2-
acetylaminopropionoyl; 2-acetylaminopropanoyl; 2-acetyl-N-methylaminoethanoyl; N,N-dimethylaminoacetyl; 2-aminobutanoyl; N-acetyl-2-aminobutanoyl; 2-amino-3-methylbutanoyl; N-acetyl-2-amino-3-methylbutanoyl; 2-amino-3,3-dimethylbutanoyl; N-acetyl-2-amino-3,3-dimethylbutanoyl; 2-amino-3-methylpentanoyl; N-acetyl-2-amino-3-methylpentanoyl; pentanoyl; 3-methylpentanoyl; 4-methylpentanoyl; 2-amino-4-methylpentanoyl; N-acetyl-2-amino-4-methylpentanoyl; 2-amino-4,4-dimethylpentanoyl; N-acetyl-2-amino-4,4-dimethylpentanoyl; 2-aminopentanoyl; N-acetyl-2-aminopentanoyl; 2-amino-5-methylhexanoyl; N-acetyl-2-amino-5-methylhexanoyl; 2-hydroxy-3-methylbutanoyl; 2-methoxy-3-methylbutanoyl; 2-hydroxy-3,3-dimethylbutanoyl; 2-methoxy-3,3-dimethylbutanoyl; 2-hydroxy-3-methylpentanoyl; 2-methoxy-3-methylpentanoyl; 2-hydroxy-4-methylpentanoyl; 2-methoxy-4-methylpentanoyl; 2-hydroxy-4,4-dimethylpentanoyl; 2-methoxy-4,4-dimethylpentanoyl; 2-

-18-

hydroxypentanoyl; 2-methoxypentanoyl; 2-hydroxy-5-methylhexanoyl; 2-methoxy-5-methylhexanoyl;

5 In cysteine protease inhibitors of general formula (I), it is preferred that in the group (X)_o, each of R¹⁶ and R¹⁷ is selected from C₀₋₇-alkyl or Ar-C₀₋₇-alkyl, for example hydrogen, a straight or branched alkyl chain, a straight or branched heteroalkyl chain, an optionally substituted arylalkyl chain or an optionally substituted arylheteroalkyl chain.

10 More preferred (X)_o groups comprise R¹⁶ chosen from hydrogen; R¹⁷ chosen from hydrogen or C₁₋₄-alkyl, which may be substituted with OH, NR²²R²², COOR²², or CONR²², or Ar-C₁₋₄-alkyl, where the aryl group may be substituted with R²¹, wherein each R²¹ and R²² is independently as defined previously.

15 Yet more preferred (X)_o groups are those in which R¹⁶ is from hydrogen and R¹⁷ is chosen from hydrogen or simple C₁₋₄-alkyl groups such as methyl, ethyl, propyl, butyl.

20 In the most preferred (X)_o groups, R¹⁶ and R¹⁷ are hydrogen and o is zero or one.

Preferred compounds of general formula (I) are those in which, in the group (W)_n, W is chosen from O, S, SO₂, S(O), C(O) or NR¹⁸, where R¹⁸ is chosen from C₀₋₇-alkyl; and n is zero or one.

25 In more preferred (W)_n groups, W comprises O, S, SO₂, C(O) or NH where n is zero or one.

Still more active compounds are those in which W is C(O) or NH where n is zero or one.

30

It is most preferred that in the group (W)_n, W is NH and n is zero or one.

-19-

In protease inhibitors of general formula (I), more active compounds are those in which, in the group (V)_m, V is chosen from C(O), OC(O), NHC(O), C(O)NH, CHR²⁰, C=N-C(O)-OR¹⁹ or C=N-C(O)-NHR¹⁹

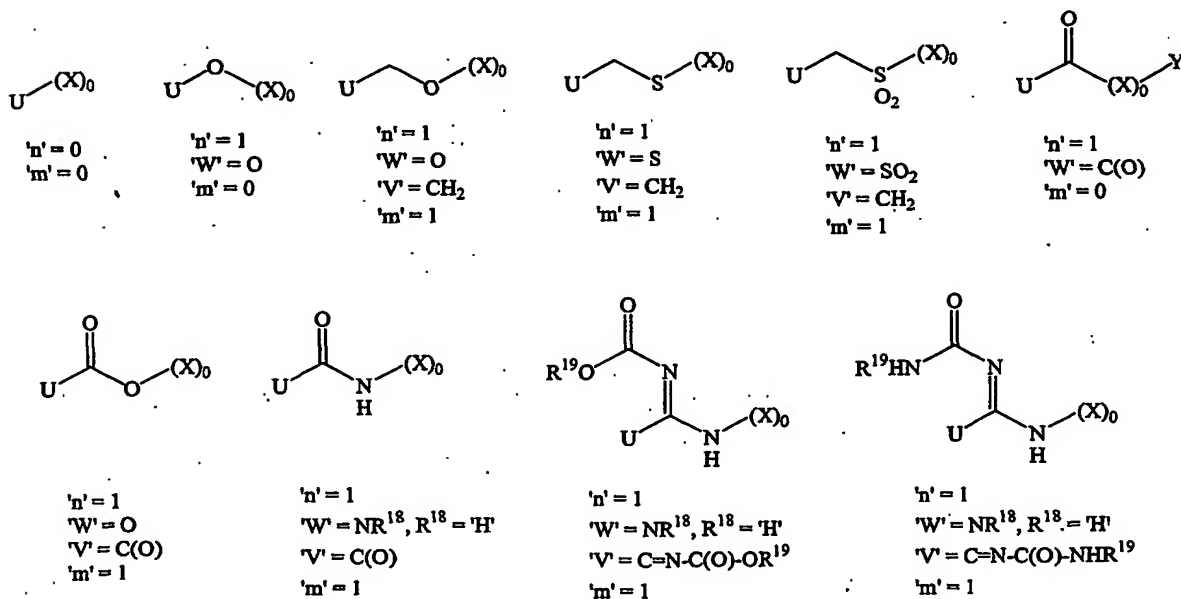
where R¹⁹ is chosen from C₀₋₇-alkyl, C₃₋₆-cycloalkyl, Ar-C₀₋₇-alkyl and R²⁰

5 is C₀₋₄-alkyl, and

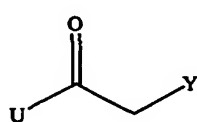
m is zero or one.

Examples of preferred V and W substituent combinations include, but are not limited to:

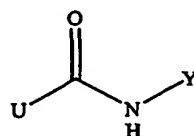
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Preferred V, W and X substituent combinations include, but are not limited to:



(X)₀ = 'CH₂'
'n' = 1
'W' = C(O)
'm' = 0



(X)₀ = 'H'
'n' = 1
'W' = NR¹⁸, R¹⁸ = 'H'
'V' = C(O)
'm' = 1

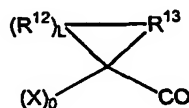
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As mentioned above, the substituents Y and U are important in determining the inhibitory potency and selectivity for various proteases and the preferred Y and U substituents vary depending on the target protease.

5

In compounds of general formula (I) that are inhibitors of cathepsin K, it is preferred that the Y substituent is CHR^{11}CO where R^{11} is selected from C_{0-7} -alkyl, Ar- C_{0-7} -alkyl or C_{3-6} -cycloalkyl. Examples of suitable R^{11} groups include, for example, hydrogen, a straight or branched alkyl chain, a straight or branched heteroalkyl chain, an optionally substituted arylalkyl chain or an optionally substituted arylheteroalkyl chain, cyclohexylmethyl or cyclopentylmethyl. Additionally, preferred compounds of general formula (I) are those in which Y comprises a group:

15



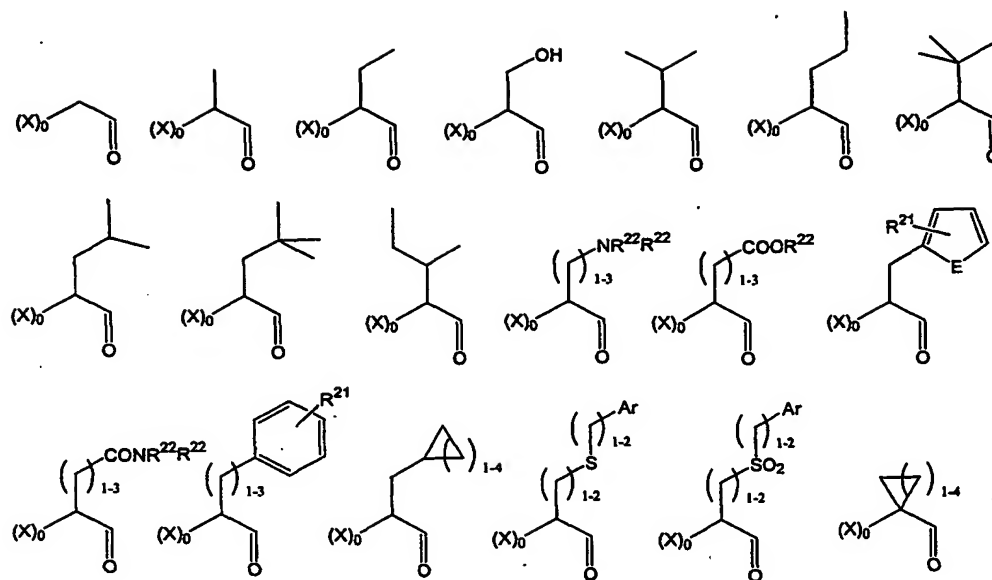
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where R^{12} and R^{13} are each $\text{CR}^{14}\text{R}^{15}$ and each R^{14} and R^{15} is, independently, selected from C_{0-7} -alkyl or Ar- C_{0-7} -alkyl, for example hydrogen, a straight or branched alkyl chain, a straight or branched heteroalkyl chain, an optionally substituted arylalkyl chain or an optionally substituted arylheteroalkyl chain and L is a number from one to four.

25

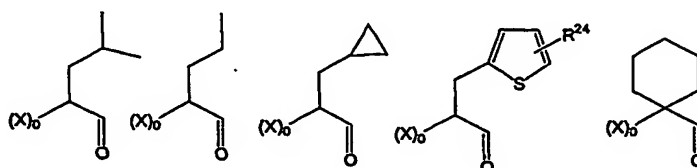
Examples of preferred Y substituents in compounds of general formula (I) which are inhibitors of cathepsin K include, but are not limited to:

-21-



wherein E, R^{21} , R^{22} and Ar are as defined previously; any of which may be substituted with one or more halogen, preferably fluoro, substituents.

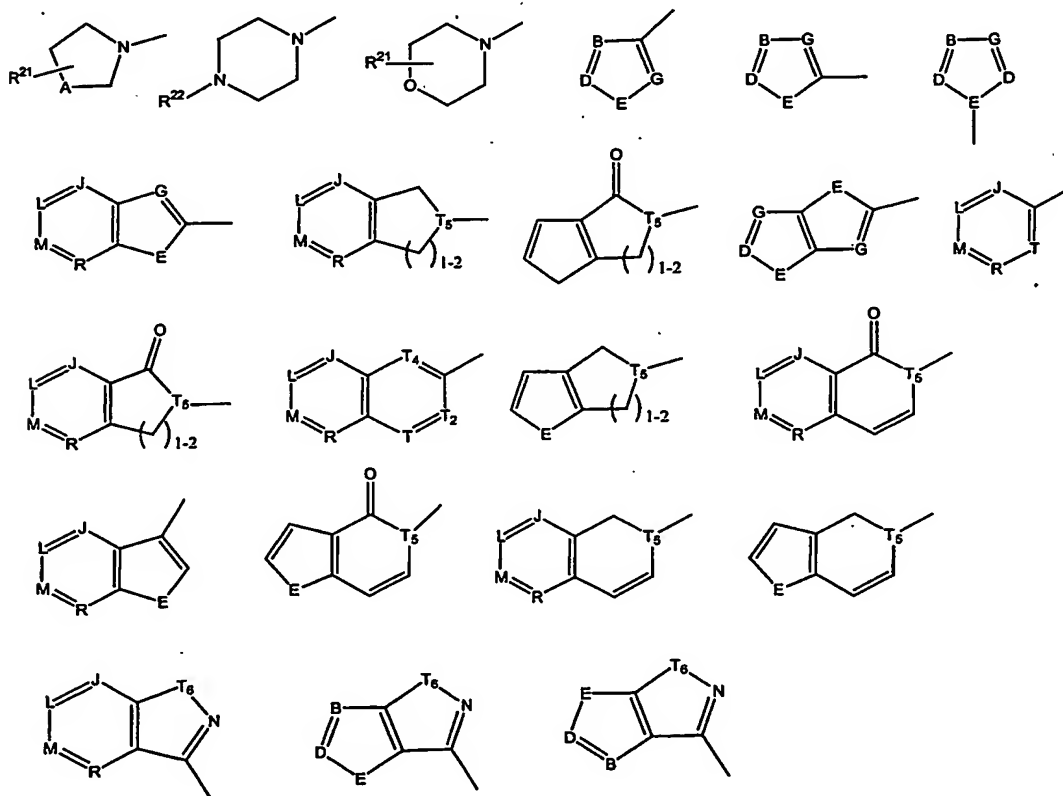
- 5 In compounds that are inhibitors of cathepsin K, more preferred R^{11} groups include C_{1-4} -alkyl, which may be substituted with cycloalkylmethyl or halogen, or R^{11} is chosen from cycloalkyl-1-carbonyl or R^{11} is chosen from Ar- C_{1-4} -alkyl, where the aryl group may be substituted with R^{21} ; where R^{21} is defined above.
- 10 Increased inhibition of cathepsin K can be achieved in compounds in which the R^{11} groups are simple branched alkyl groups such as isobutyl or straight alkyl chains such as n-propyl, optionally substituted with one or more halogen (preferably fluoro) substituents. Yet more preferred R^{11} groups comprise ArCH₂- , where the aromatic ring is an optionally substituted monocyclic heterocycle and
- 15 still more preferred R^{11} groups comprise cyclopropylmethyl and cyclohexyl-1-carbonyl. In compounds which are particularly active inhibitors of cathepsin K, Y substituents include, but are not limited to:



-22-

wherein R^{24} is chosen from hydrogen, methyl, methoxy, ethyl, isopropyl, F, Cl and wherein any of the alkyl groups may be substituted with one or more F or Cl.

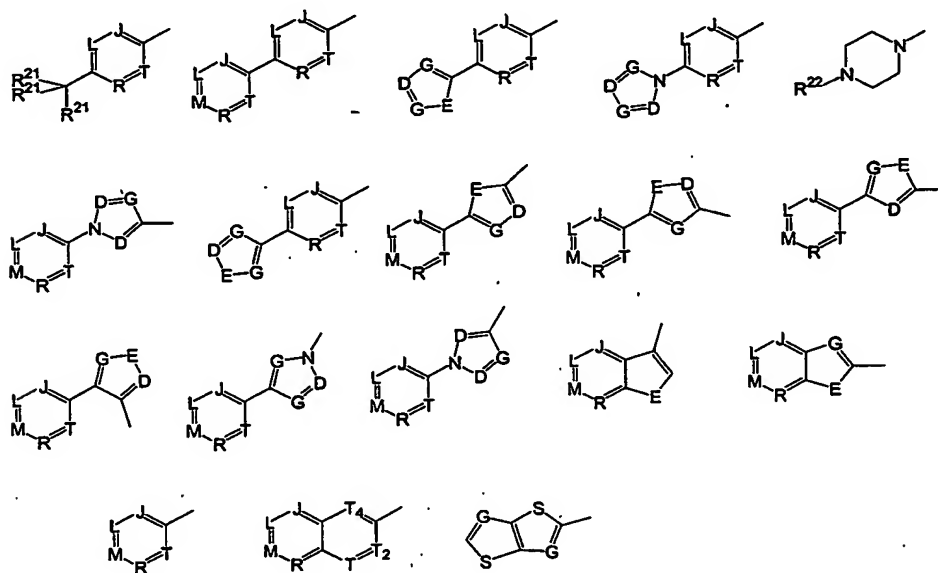
- 5 In order to maximise the inhibition of cathepsin K, the compound of formula (I) may comprise R^{11} groups which are simple branched alkyl groups such as isobutyl or n-propyl or halogen substituted variants thereof such as 3,3,3-trifluoro-2-trifluoromethylpropyl.
- 10 In compounds of general formula (I) that are inhibitors of cathepsin K, it is preferred that the group U comprises an optionally substituted 5- or 6-membered saturated or unsaturated heterocycle or Ar group or an optionally substituted saturated or unsaturated 8 to 10-membered heterocycle or Ar group. Examples of such preferred U rings include, but are not limited to the following:



-23-

wherein R^{21} , R^{22} , A, B, D, E, G, J, L, M, R, T, T_2 , T_4 , T_5 and T_6 are as defined previously.

Stronger inhibition of cathepsin K can be achieved in compounds where the U groups comprise a bulky alkyl or aryl group at the para position of an aryl; a meta or para 5,6-biaryl Ar-Ar, where Ar is as previously defined; a 6,6 or 6,5 or 5,5-fused aromatic ring, where Ar is as previously defined, or a 4-substituted piperazine. Examples of more preferred U groups include but are not limited to:



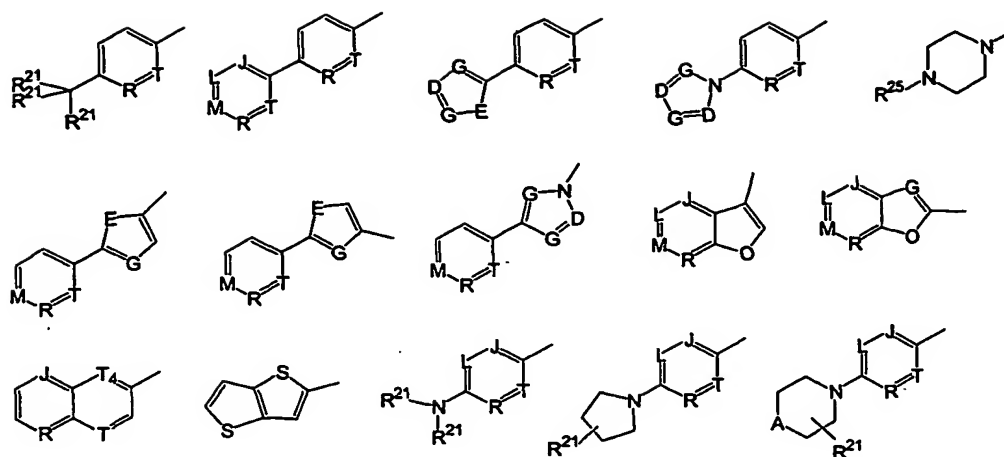
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wherein R^{21} , R^{22} , D, E, G, J, L, M, R, T, T_2 and T_4 are as defined previously.

In compounds that are inhibitors of cathepsin K, even more preferred U groups comprise a 6-membered aromatic ring Ar containing a bulky alkyl or aryl group at the para position; a meta or para-biaryl Ar-Ar, where Ar is as previously defined; a 6,6 or 6,5 or 5,5-fused aromatic ring, where Ar is as previously defined; or a 4-substituted piperazine where R²⁵ is chosen from hydrogen, C₁₋₂-alkyl or Ar-C₀₋₂-alkyl. Examples of even more preferred U groups include but are not limited to:

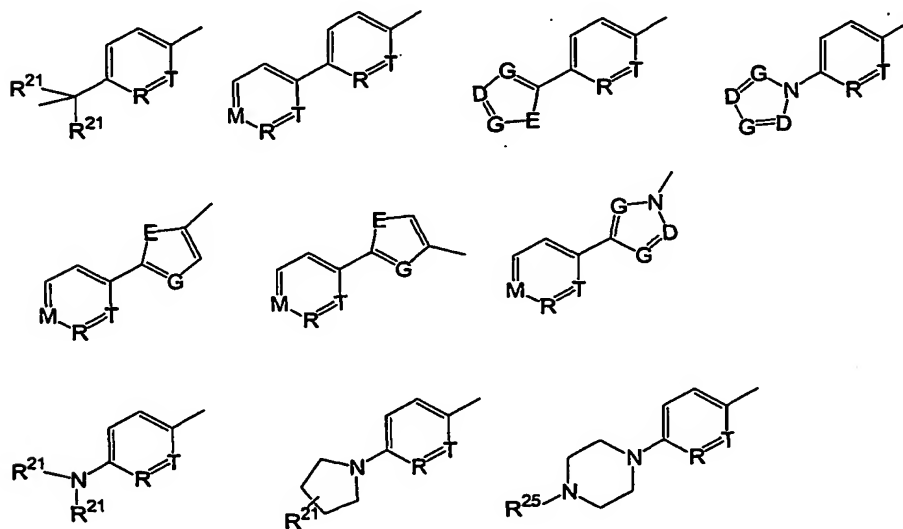
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-24-



wherein R^{21} , R^{25} , D, E, G, J, L, M, R, T and T_4 are as defined previously.

- 5 In order to maximise inhibition of cathepsin K, compounds of general formula (I) may be selected to have U groups chosen from the following:

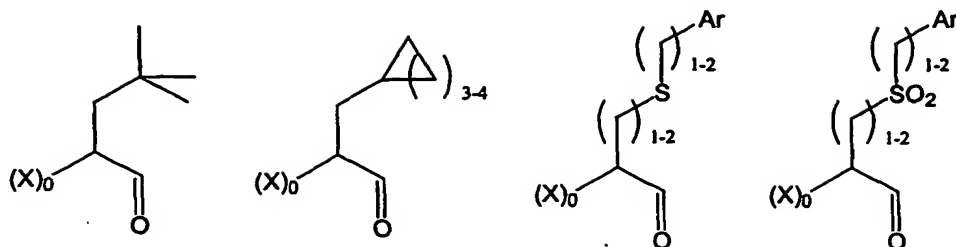


wherein R^{21} , R^{25} , D, E, G, M, R and T are as defined previously.

10

In order to achieve the greatest inhibitory effect against cathepsin S, it is preferred that the Y substituent is chosen from the following;

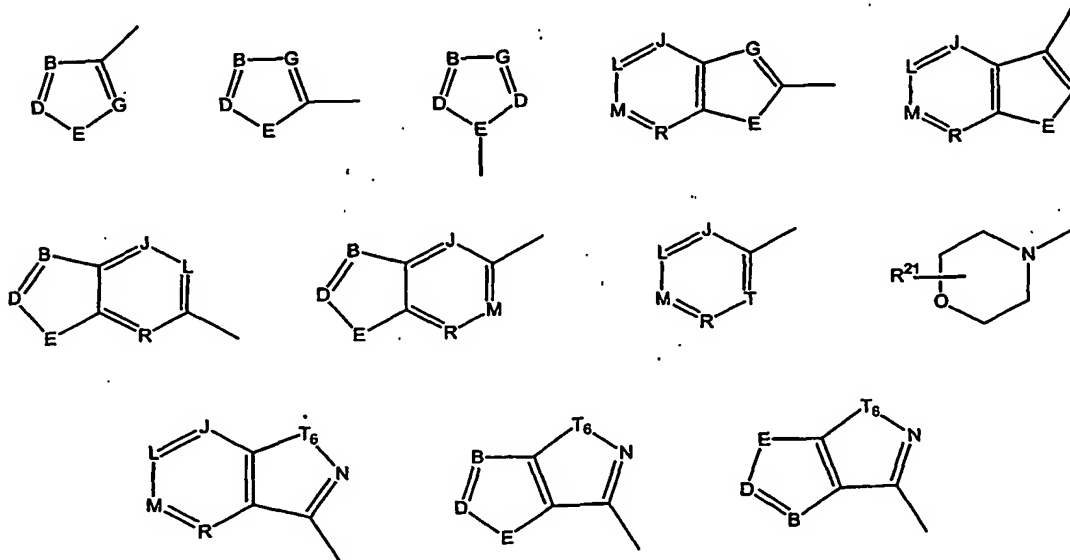
-25-



wherein $(X)_0$ and Ar are as previously defined.

- 5 In order to achieve the greatest inhibitory effect against cathepsin S, it is preferred that the group U comprises an optionally substituted 5-membered unsaturated heterocycle or a 6,5- 5,5- or 5,6-fused aromatic ring, where Ar is as previously defined or a morpholine. Examples of such preferred U rings include, but are not limited to the following:

10

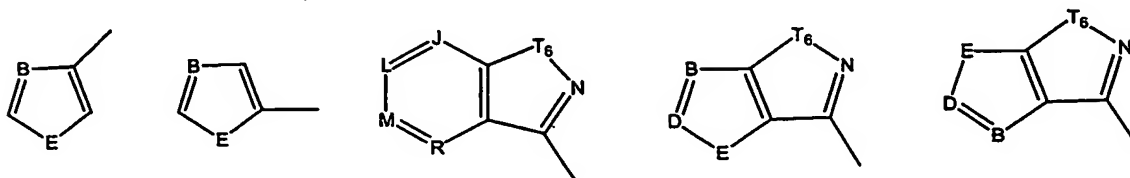


wherein R^{21} , B, D, E, G, J, L, M, R and T_6 are as defined previously.

- 15 In order to achieve the greatest inhibitory effect against cathepsin S whilst retaining selectivity against other CA C1 cysteinyl proteases, it is more preferred that the group U comprises an optionally substituted 5-membered unsaturated

-26-

heterocycle or a 6,5- or 5,5-fused aromatic ring, where Ar is as previously defined. Examples of more preferred U rings include, but are not limited to the following:

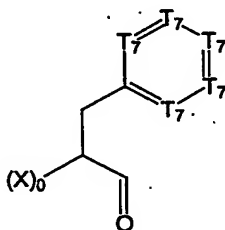


5

wherein B, D, E, J, L, M, R and T₆ are as defined previously.

In order to achieve the greatest inhibitory effect against cathepsin L, it is preferred that the Y substituent is chosen as an aromatic group as follows;

10



wherein T₇ is chosen from CH, N or CR²¹ where R²¹ is as defined previously.

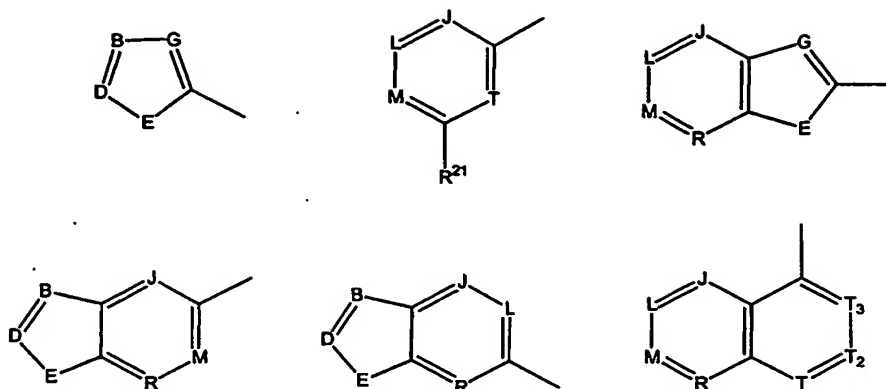
In particular, for cathepsin L inhibition it is more preferred that within the T₇ substituent that the R²¹ substituent is chosen from single and multiple ring substitution combinations of Me, F, Cl, OH and OMe.

15

In order to achieve the greatest inhibitory effect against cathepsin L, it is preferred that the group U comprises an optionally substituted 5-membered unsaturated heterocycle or a 6,6- or 6,5- or 5,6-fused aromatic ring, where Ar is as previously defined or a meta-substituted Ar. Examples of such preferred U rings include, but are not limited to the following:

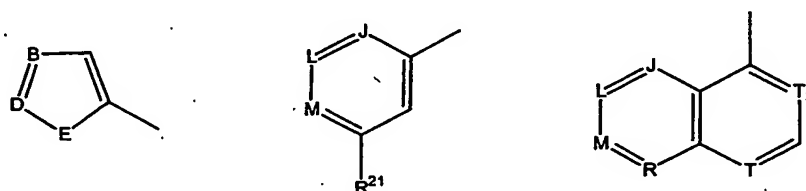
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-27-



wherein R^{21} , B, D, E, G, J, L, M, R, T, T_2 and T_3 are as defined previously.

In order to achieve the greatest inhibitory effect against cathepsin L whilst retaining selectivity against other CA C1 cysteinyl proteases, it is more preferred that the group U comprises a substituted 5-membered unsaturated heterocycle or a 6,6-fused aromatic ring, where Ar is as previously defined or a meta-substituted Ar. Examples of such preferred U rings include, but are not limited to the following:



wherein E is chosen from oxygen or N-ethyl, D is chosen from nitrogen or CCH_3 , B is chosen from nitrogen or CCH_3 , R^{21} is chosen from halogen, OMe, CF_3 , OCF_3 , CH_2NH_2 and J, L, M, R, T and T_3 are as previously defined.

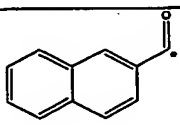
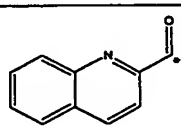
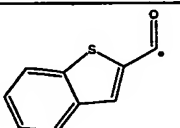
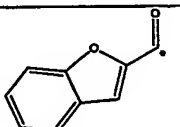
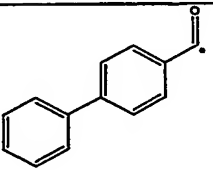
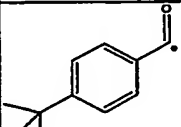
The inventors have observed that for the cruzipains and *leishmania mexicana* CPB protease, that the U and Y substituent preferences are composed of a mixture of those described earlier for cathepsin K and cathepsin L. In essence, many of the preferred cathepsin K and cathepsin L inhibitors also show potency against the cruzipains and *leishmania mexicana* CPB protease as highlighted in the

-28-

EXAMPLES section. Such promiscuity can be used to provide potent and selective inhibitors of the cruzipains and *leishmania mexicana* CPB protease by combining a preferred U substituent as described for cathepsin K with a preferred Y substituent as described for cathepsin L or by combining a preferred U substituent as described for cathepsin L with a preferred Y substituent as described for cathepsin K. Such preferred combinations provide potent inhibitors of the cruzipains and *leishmania mexicana* CPB protease with selectivity against either or both cathepsin K and cathepsin L.

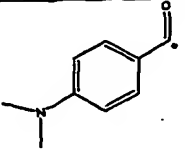
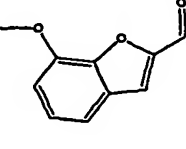
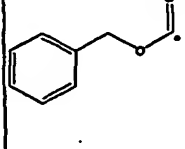
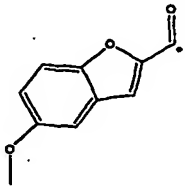
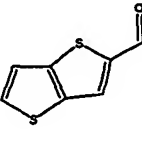
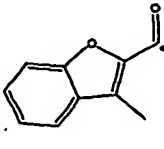
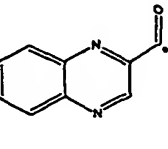
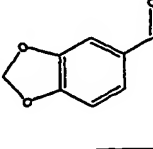
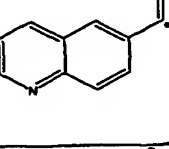
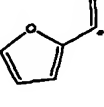
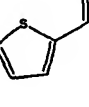
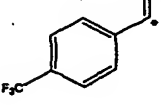
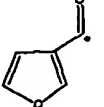
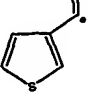
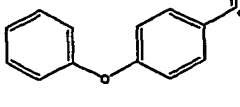
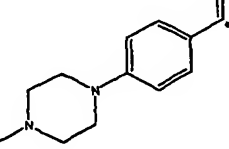
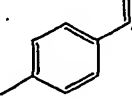
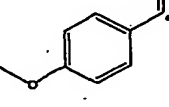
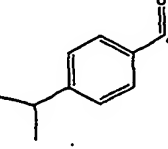
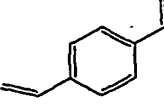
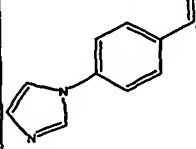
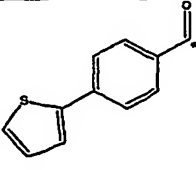
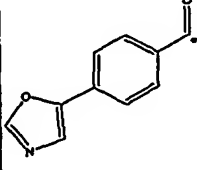
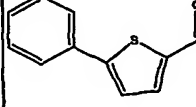
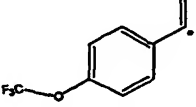
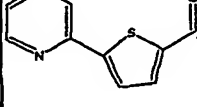
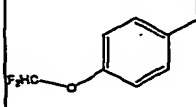
Particular compounds of the invention are selected from the compounds formed by joining one of the 'U-(V)_m' fragments herein defined as the 'Capping group (Cg1 to Cg103)' of general formula (I) shown in Table 1, with one of the '(W)_n-(X)_o-Y' fragments herein defined as the 'P2 pocket group (Pg1 to Pg39)' of general formula (I) shown in Table 2, with a 5,5-bicyclic scaffold containing one of the R¹ fragments herein defined as the 'Prime-side binding group (Ps1 to Ps243)' of general formula (I) shown in Table 3.

Table (1) 'Capping group Cg' Fragments

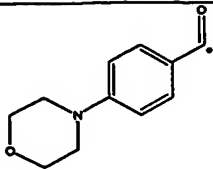
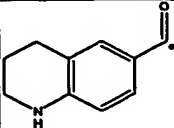
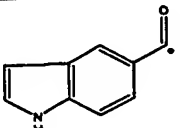
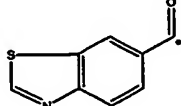
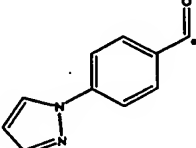
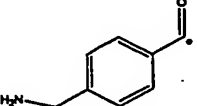
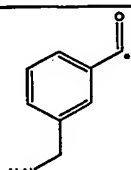
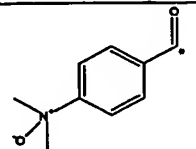
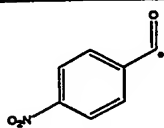
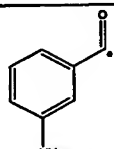
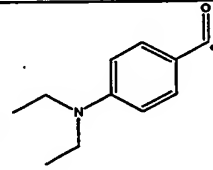
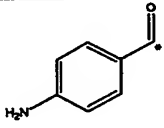
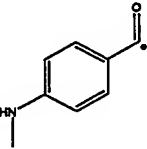
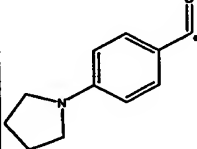
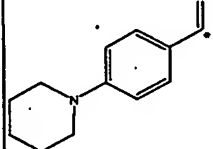
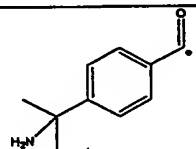
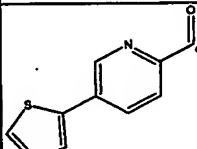
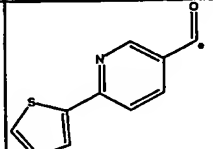
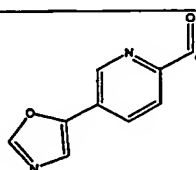
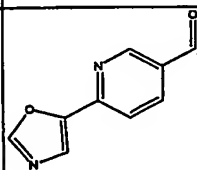
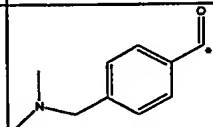
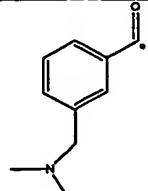
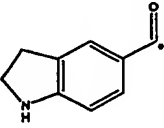
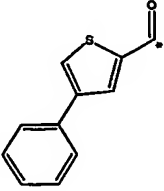
	U-(V) _m		U-(V) _m		U-(V) _m
Cg1		Cg2		Cg3	
Cg4		Cg5		Cg6	

* signifies the point of attachment of 'Cg groups' to 'Pg groups'.

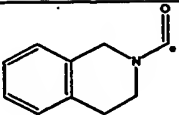
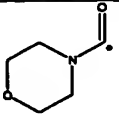
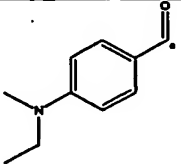
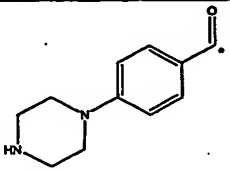
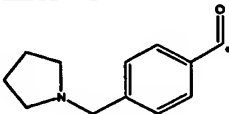
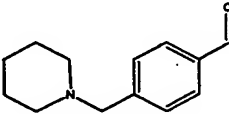
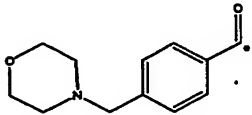
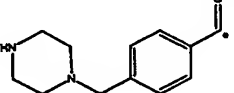
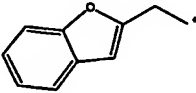
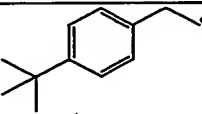
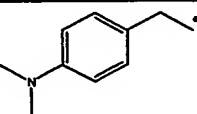
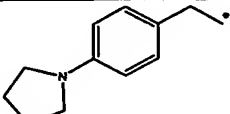
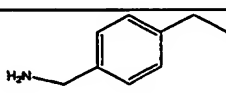
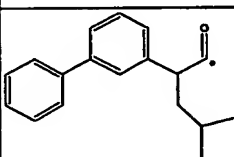
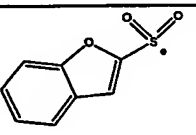
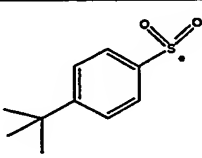
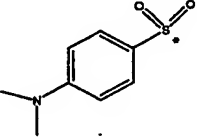
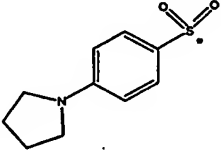
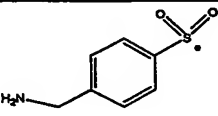
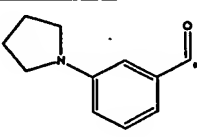
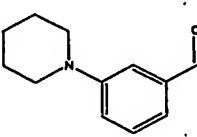
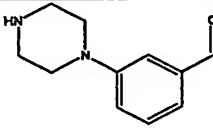
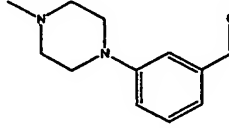
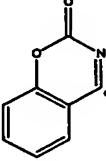
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Cg7		Cg8		Cg9	
Cg10		Cg11		Cg12	
Cg13		Cg14		Cg15	
Cg16		Cg17		Cg18	
Cg19		Cg20		Cg21	
Cg22		Cg23		Cg24	
Cg25		Cg26		Cg27	
Cg28		Cg29		Cg30	
Cg31		Cg32		Cg33	

-30-

Cg34		Cg35		Cg36	
Cg37		Cg38		Cg39	
Cg40		Cg41		Cg42	
Cg43		Cg44		Cg45	
Cg46		Cg47		Cg48	
Cg49		Cg50		Cg51	
Cg52		Cg53		Cg54	
Cg55		Cg56		Cg57	

-31-

Cg58		Cg59		Cg60	
Cg61		Cg62		Cg63	
Cg64		Cg65		Cg66	
Cg67		Cg68		Cg69	
Cg70		Cg71		Cg72	
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Cg76		Cg77		Cg78	
Cg79		Cg80		Cg81	

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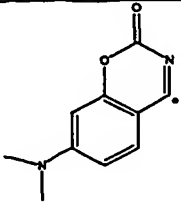
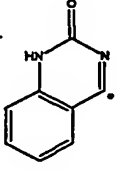
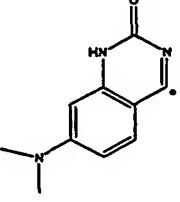
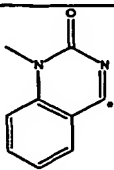
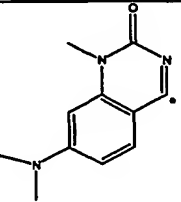
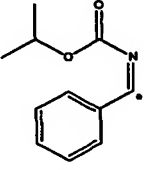
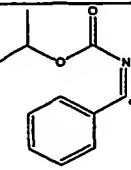
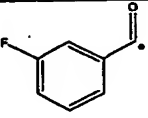
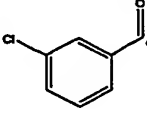
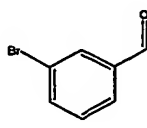
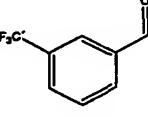
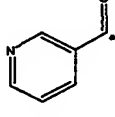
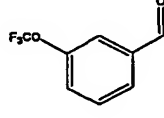
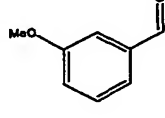
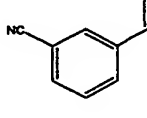
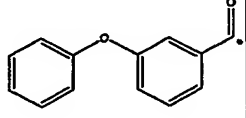
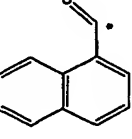
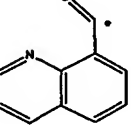
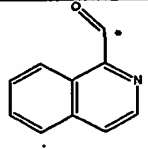
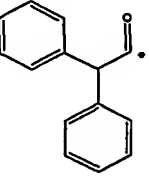
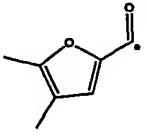
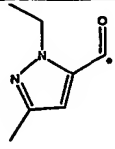
Cg82		Cg83		Cg84	
Cg85		Cg86		Cg87	
Cg88		Cg89		Cg90	
Cg91		Cg92		Cg93	
Cg94		Cg95		Cg96	
Cg97		Cg98		Cg99	
Cg100		Cg101		Cg102	
Cg103					

Table (2) 'P2 pocket group Pg' Fragments

** signifies the point of attachment of 'Pg groups' to 5,5-bicyclic scaffold.

	(W) _n -(X) _o -Y		(W) _n -(X) _o -Y		(W) _n -(X) _o -Y
Pg1		Pg2		Pg3	
Pg4		Pg5		Pg6	
Pg7		Pg8		Pg9	
Pg10		Pg11		Pg12	
Pg13		Pg14		Pg15	
Pg16		Pg17		Pg18	

-34-

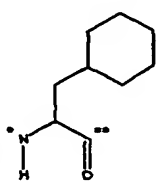
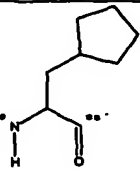
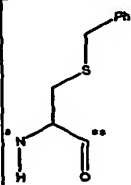
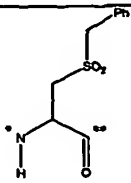
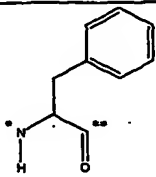
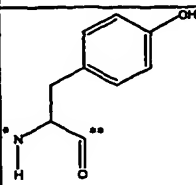
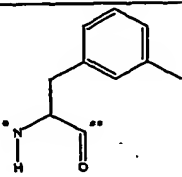
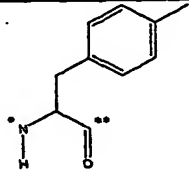
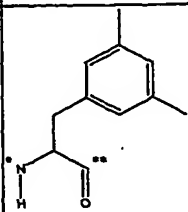
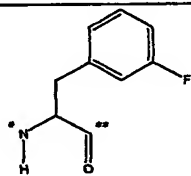
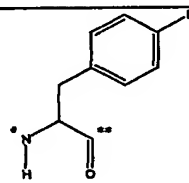
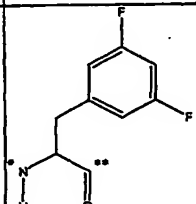
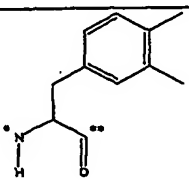
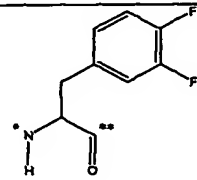
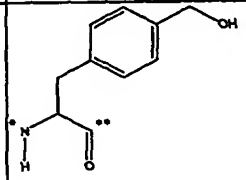
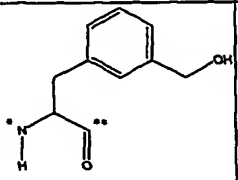
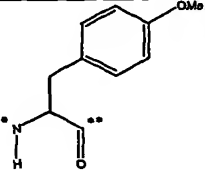
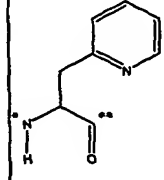
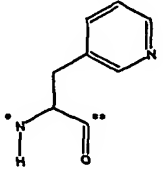
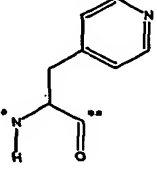
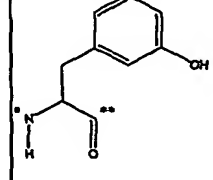
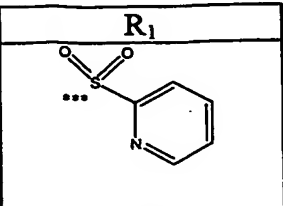
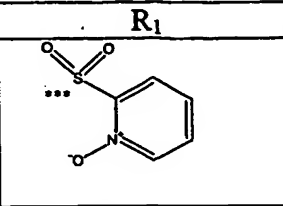
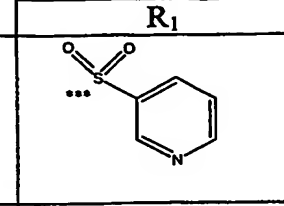
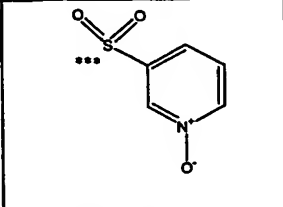
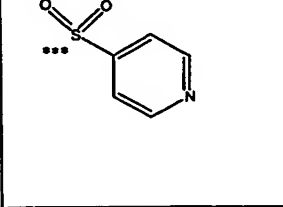
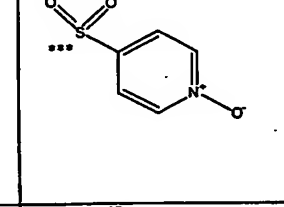
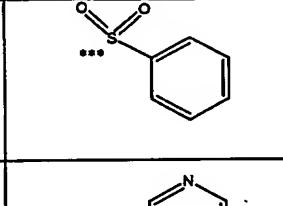
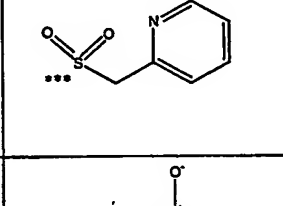
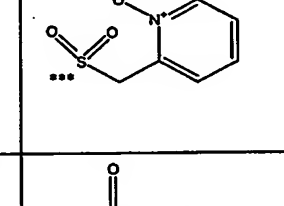
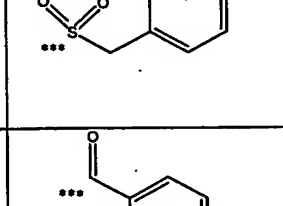
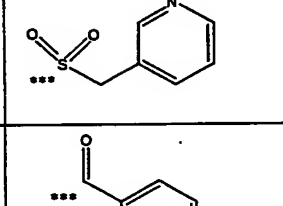
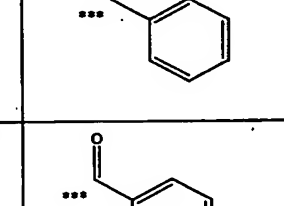
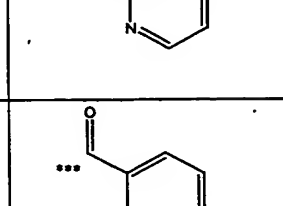
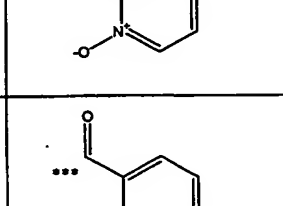
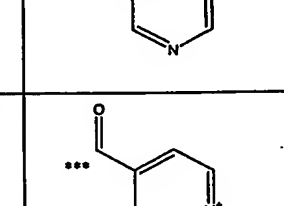
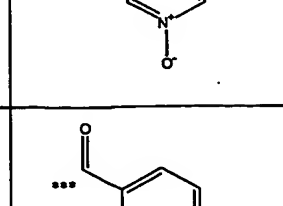
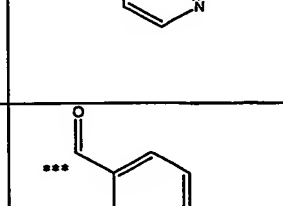
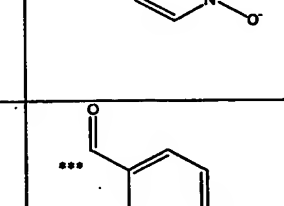
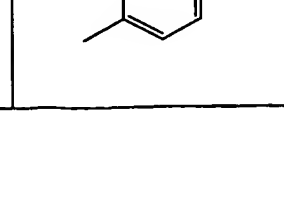
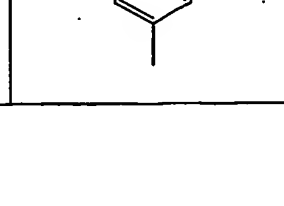

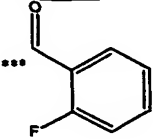
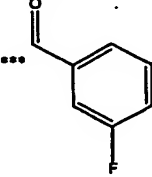
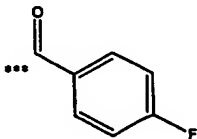
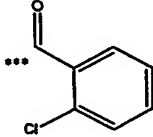
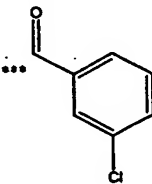
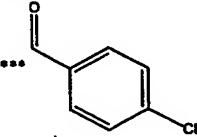
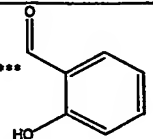
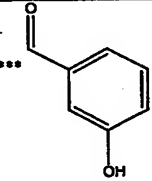
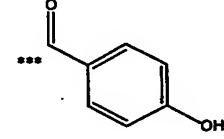
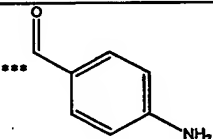
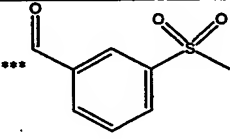
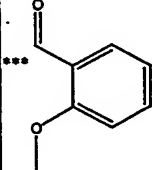
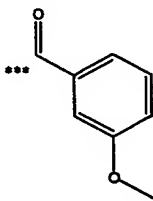
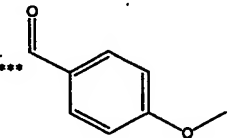
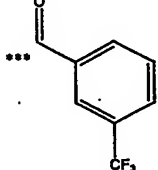
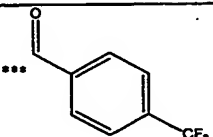
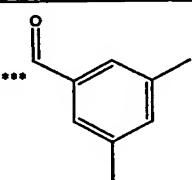
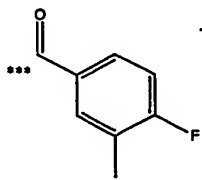
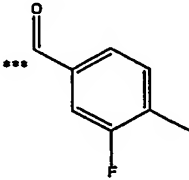
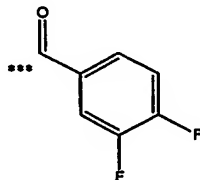
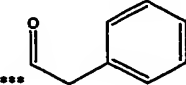
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Pg22		Pg23		Pg24	
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Pg28		Pg29		Pg30	
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Pg37		Pg38		Pg39	

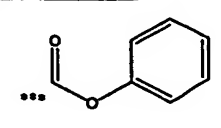
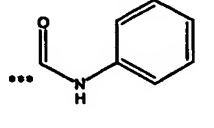
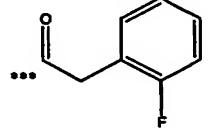
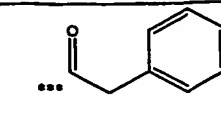
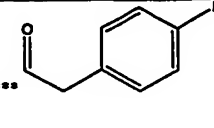
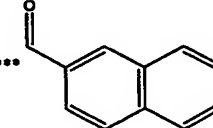
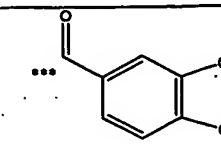
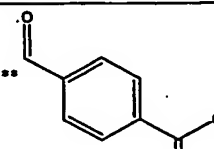
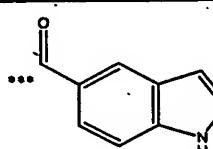
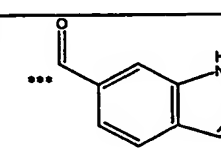
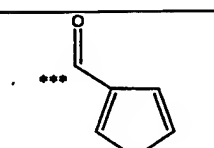
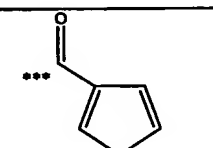
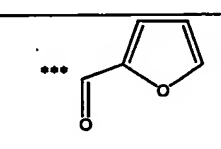
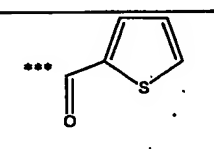
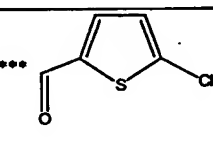
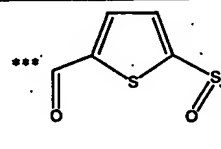
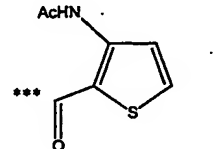
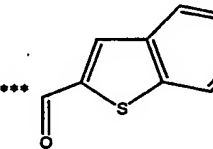
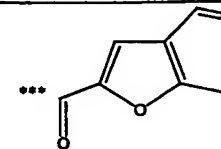
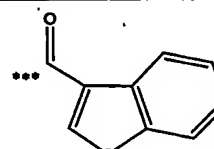
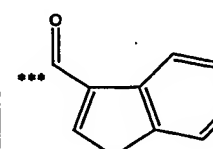
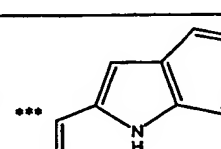
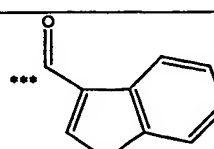
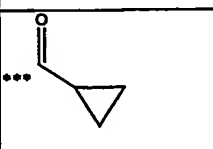
Table (3) 'Prime-side binding group Ps' Fragments

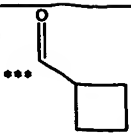
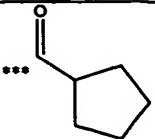
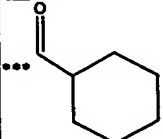
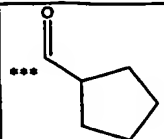
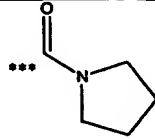
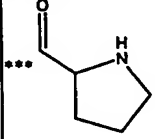
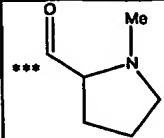
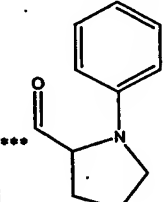
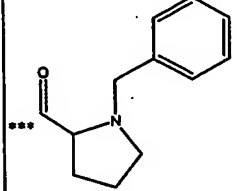
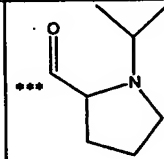
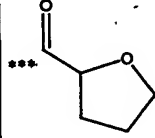
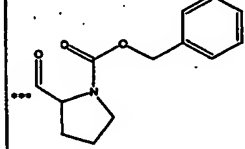
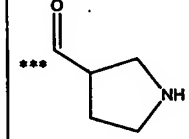
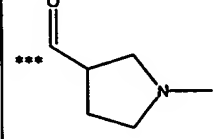
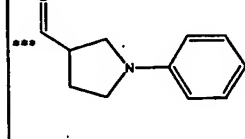
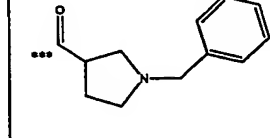
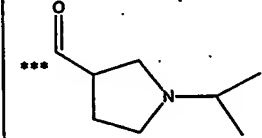
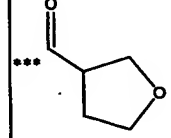
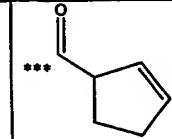
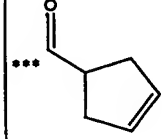
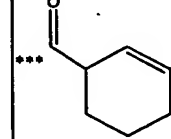
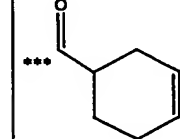
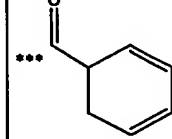
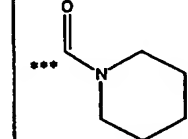
*** signifies the point of attachment of 'Ps groups' to 5,5-bicyclic scaffold.

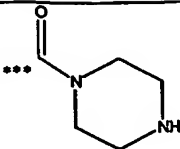
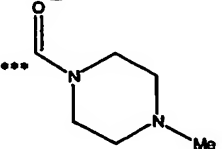
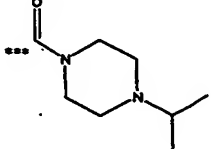
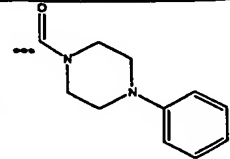
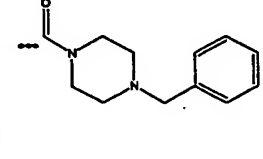
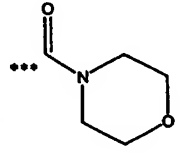
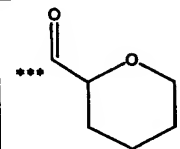
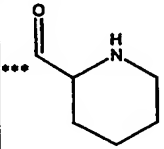
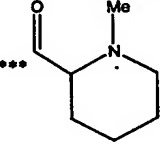
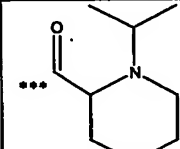
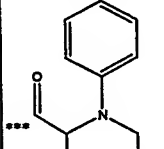
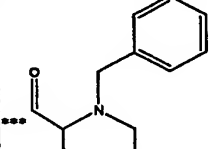
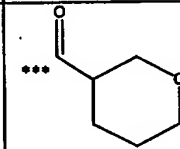
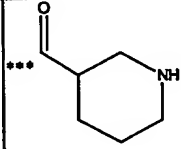
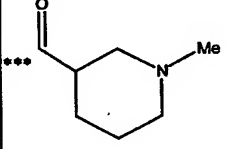
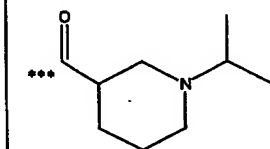
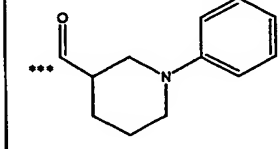
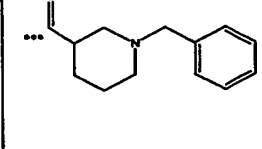
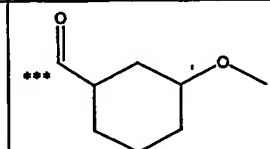
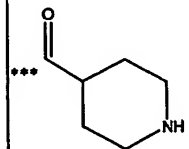
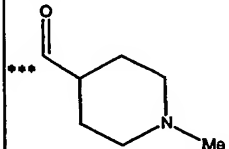
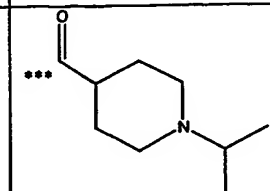
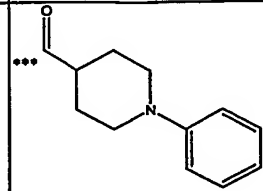
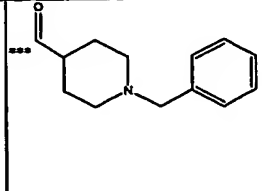
Ps1		Ps2		Ps3	
Ps4		Ps5		Ps6	
Ps7		Ps8		Ps9	
Ps10		Ps11		Ps12	
Ps13		Ps14		Ps15	
Ps16		Ps17		Ps18	
Ps19		Ps20		Ps21	

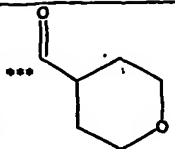

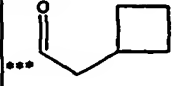
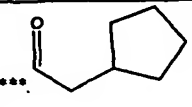
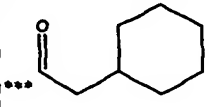
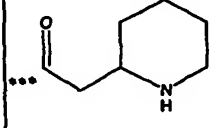
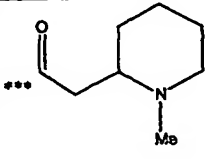
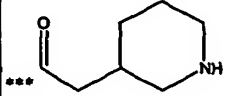
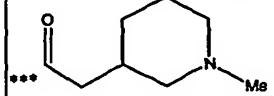
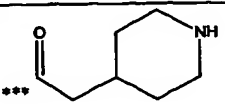
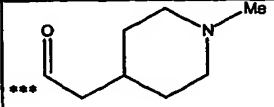
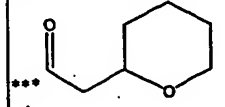
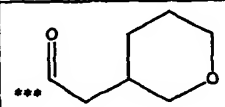
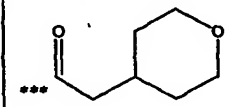
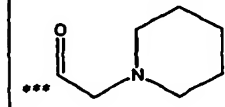
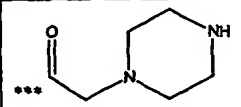
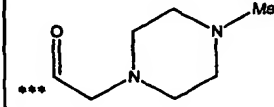
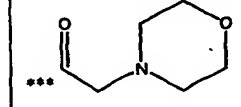
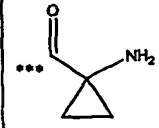
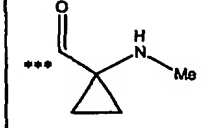
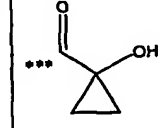
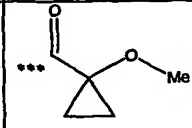
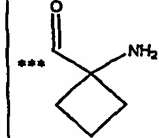
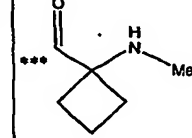
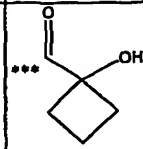
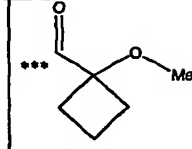
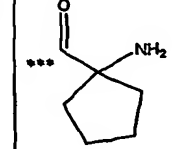
-36-

Ps22		Ps23		Ps24	
Ps25		Ps26		Ps27	
Ps28		Ps29		Ps30	
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Ps34		Ps35		Ps36	
Ps37		Ps38		Ps39	
Ps40		Ps41		Ps42	

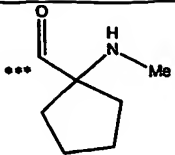
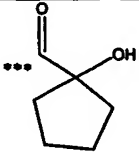
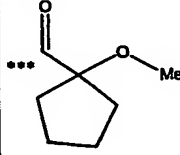
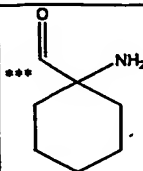
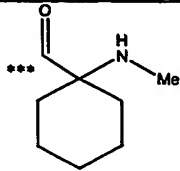
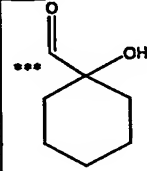
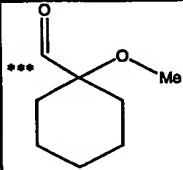
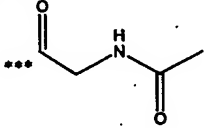
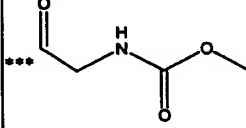
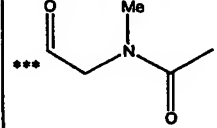
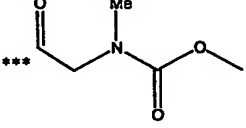
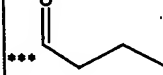
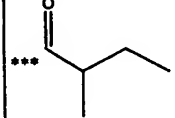
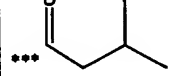
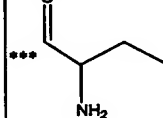
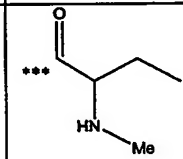
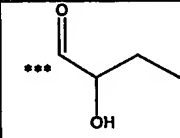
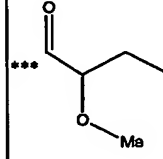
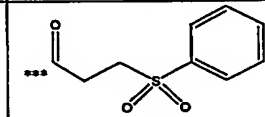
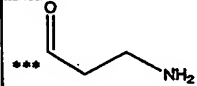
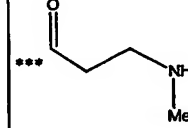
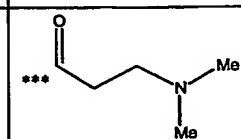
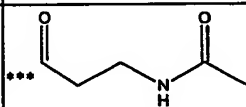
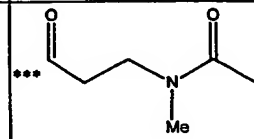
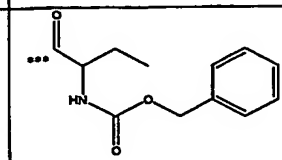
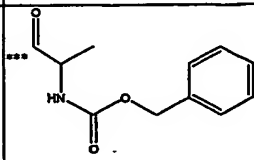
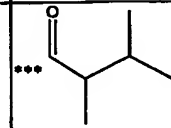
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Ps46		Ps47		Ps48	
Ps49		Ps50		Ps51	
Ps52		Ps53		Ps54	
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Ps58		Ps59		Ps60	
Ps61		Ps62		Ps63	
Ps64		Ps65		Ps66	

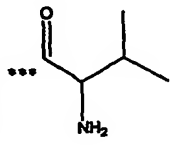
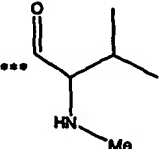
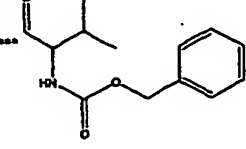
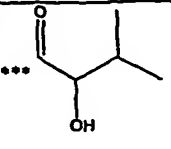
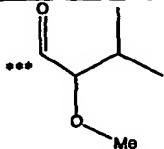
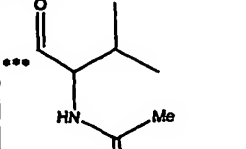
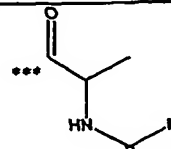
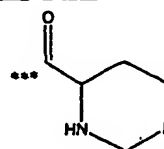
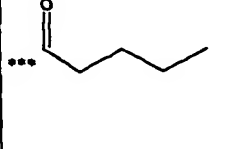
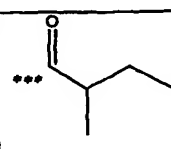
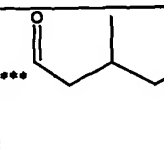
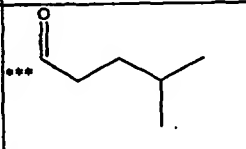
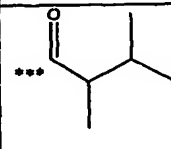
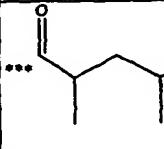
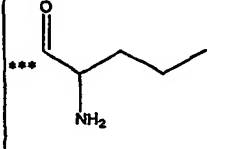
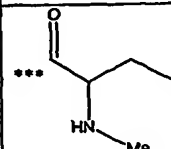
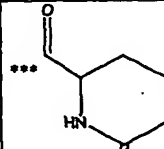
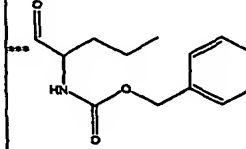
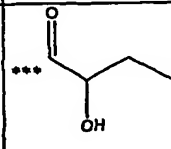
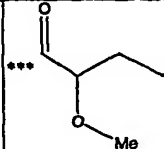
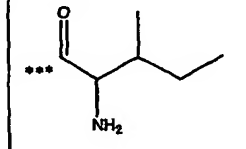
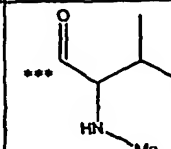
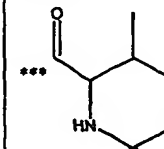
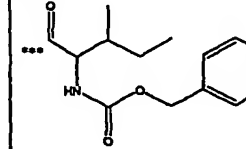
Ps67		Ps68		Ps69	
Ps70		Ps71		Ps72	
Ps73		Ps74		Ps75	
Ps76		Ps77		Ps78	
Ps79		Ps80		Ps81	
Ps82		Ps83		Ps84	
Ps85		Ps86		Ps87	
Ps88		Ps89		Ps90	

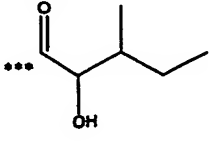
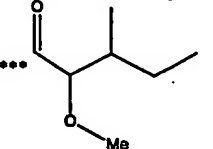
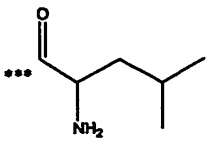
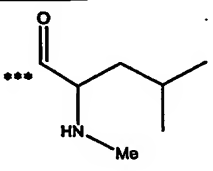
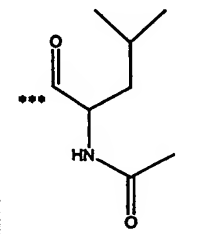
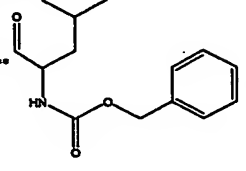
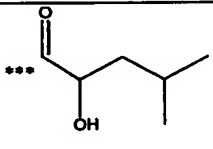
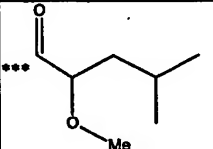
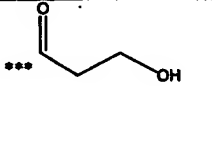
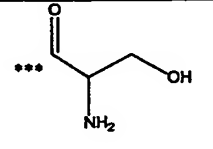
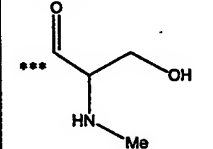
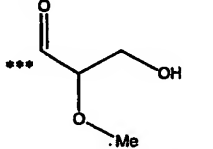
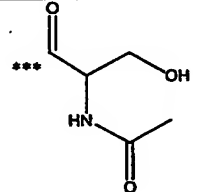
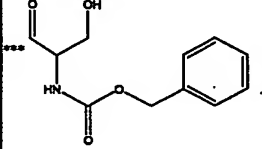
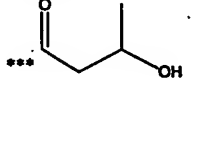
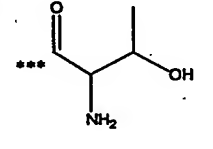
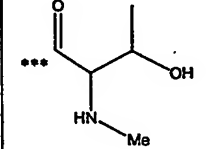
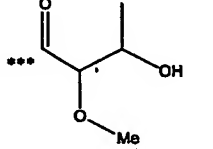
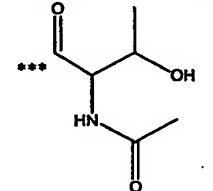
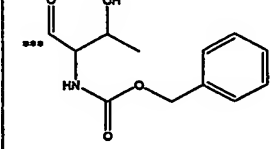
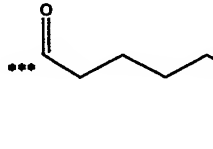
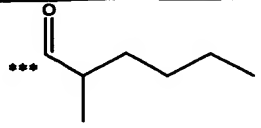
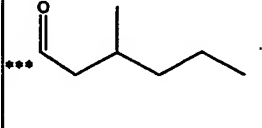
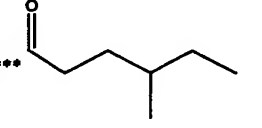
Ps91		Ps92		Ps93	
Ps94		Ps95		Ps96	
Ps97		Ps98		Ps99	
Ps100		Ps101		Ps102	
Ps103		Ps104		Ps105	
Ps106		Ps107		Ps108	
Ps109		Ps110		Ps111	
Ps112		Ps113		Ps114	

Ps115		Ps116		Ps117	
Ps118		Ps119		Ps120	
Ps121		Ps122		Ps123	
Ps124		Ps125		Ps126	
Ps127		Ps128		Ps129	
Ps130		Ps131		Ps132	
Ps133		Ps134		Ps135	
Ps136		Ps137		Ps138	
Ps139		Ps140		Ps141	

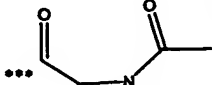
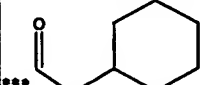
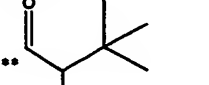
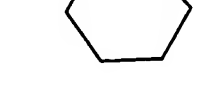
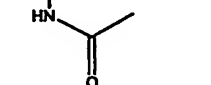

-41-

Ps142		Ps143		Ps144	
Ps145		Ps146		Ps147	
Ps148		Ps149		Ps150	
Ps151		Ps152		Ps153	
Ps154		Ps155		Ps156	
Ps157		Ps158		Ps159	
Ps160		Ps161		Ps162	
Ps163		Ps164		Ps165	
Ps166		Ps167		Ps168	

Ps169		Ps170		Ps171	
Ps172		Ps173		Ps174	
Ps175		Ps176		Ps177	
Ps178		Ps179		Ps180	
Ps181		Ps182		Ps183	
Ps184		Ps185		Ps186	
Ps187		Ps188		Ps189	
Ps190		Ps191		Ps192	

Ps193	 <chem>CC(C)CC(O)C=O</chem>	Ps194	 <chem>CC(C)CC(OC)C=O</chem>	Ps195	 <chem>CC(C)CC(N)C=O</chem>
Ps196	 <chem>CC(C)CC(C)CNC(C)C=O</chem>	Ps197	 <chem>CC(C)CC(C)CNC(C)C(=O)C</chem>	Ps198	 <chem>CC(C)CC(C)CNC(=O)OCC1=CC=CC=C1</chem>
Ps199	 <chem>CC(C)CC(O)C=O</chem>	Ps200	 <chem>CC(C)CC(OC)C=O</chem>	Ps201	 <chem>CC(C)CC(O)C=O</chem>
Ps202	 <chem>CC(C)CC(N)C=O</chem>	Ps203	 <chem>CC(C)CC(C)CNC(C)C=O</chem>	Ps204	 <chem>CC(C)CC(OC)C=O</chem>
Ps205	 <chem>CC(C)CC(C)CNC(C)C(=O)C</chem>	Ps206	 <chem>CC(C)CC(C)CNC(=O)OCC1=CC=CC=C1</chem>	Ps207	 <chem>CC(C)CC(O)C=O</chem>
Ps208	 <chem>CC(C)CC(N)C=O</chem>	Ps209	 <chem>CC(C)CC(C)CNC(C)C=O</chem>	Ps210	 <chem>CC(C)CC(OC)C=O</chem>
Ps211	 <chem>CC(C)CC(C)CNC(C)C(=O)C</chem>	Ps212	 <chem>CC(C)CC(C)CNC(=O)OCC1=CC=CC=C1</chem>	Ps213	 <chem>CC(C)CC(O)C=O</chem>
Ps214	 <chem>CC(C)CC(O)C=O</chem>	Ps215	 <chem>CC(C)CC(O)C=O</chem>	Ps216	 <chem>CC(C)CC(O)C=O</chem>

Ps217		Ps218		Ps219	
Ps220		Ps221		Ps222	
Ps223		Ps224		Ps225	
Ps226		Ps227		Ps228	
Ps229		Ps230		Ps231	
Ps232		Ps233		Ps234	
Ps235		Ps236		Ps237	

Ps238		Ps239		Ps240	
Ps241		Ps242		Ps243	

Particularly preferred compounds of the invention are inhibitors of cathepsin K and include but are not limited to the compounds formed by the following Cg-Pg-Ps combinations:

	Cg5-Pg1-Ps1	Cg5-Pg1-Ps2	Cg5-Pg1-Ps3	Cg5-Pg1-Ps4
	Cg5-Pg1-Ps5	Cg5-Pg1-Ps6	Cg5-Pg1-Ps7	Cg5-Pg1-Ps8
	Cg5-Pg1-Ps9	Cg5-Pg1-Ps10	Cg5-Pg1-Ps11	Cg5-Pg1-Ps12
10	Cg5-Pg1-Ps13	Cg5-Pg1-Ps14	Cg5-Pg1-Ps15	Cg5-Pg1-Ps16
	Cg5-Pg1-Ps17	Cg5-Pg1-Ps18	Cg5-Pg1-Ps19	Cg5-Pg1-Ps20
	Cg5-Pg1-Ps21	Cg5-Pg1-Ps22	Cg5-Pg1-Ps23	Cg5-Pg1-Ps24
	Cg5-Pg1-Ps25	Cg5-Pg1-Ps26	Cg5-Pg1-Ps27	Cg5-Pg1-Ps28
	Cg5-Pg1-Ps29	Cg5-Pg1-Ps30	Cg5-Pg1-Ps31	Cg5-Pg1-Ps32
15	Cg5-Pg1-Ps33	Cg5-Pg1-Ps34	Cg5-Pg1-Ps35	Cg5-Pg1-Ps36
	Cg5-Pg1-Ps37	Cg5-Pg1-Ps38	Cg5-Pg1-Ps39	Cg5-Pg1-Ps40
	Cg5-Pg1-Ps41	Cg5-Pg1-Ps42	Cg5-Pg1-Ps43	Cg5-Pg1-Ps44
	Cg5-Pg1-Ps45	Cg5-Pg1-Ps46	Cg5-Pg1-Ps47	Cg5-Pg1-Ps48
	Cg5-Pg1-Ps49	Cg5-Pg1-Ps50	Cg5-Pg1-Ps51	Cg5-Pg1-Ps52
20	Cg5-Pg1-Ps53	Cg5-Pg1-Ps54	Cg5-Pg1-Ps55	Cg5-Pg1-Ps56
	Cg5-Pg1-Ps57	Cg5-Pg1-Ps58	Cg5-Pg1-Ps59	Cg5-Pg1-Ps60
	Cg5-Pg1-Ps61	Cg5-Pg1-Ps62	Cg5-Pg1-Ps63	Cg5-Pg1-Ps64
	Cg5-Pg1-Ps65	Cg5-Pg1-Ps66	Cg5-Pg1-Ps67	Cg5-Pg1-Ps68
	Cg5-Pg1-Ps69	Cg5-Pg1-Ps70	Cg5-Pg1-Ps71	Cg5-Pg1-Ps72
25	Cg5-Pg1-Ps73	Cg5-Pg1-Ps74	Cg5-Pg1-Ps75	Cg5-Pg1-Ps76
	Cg5-Pg1-Ps77	Cg5-Pg1-Ps78	Cg5-Pg1-Ps79	Cg5-Pg1-Ps80
	Cg5-Pg1-Ps81	Cg5-Pg1-Ps82	Cg5-Pg1-Ps83	Cg5-Pg1-Ps84
	Cg5-Pg1-Ps85	Cg5-Pg1-Ps86	Cg5-Pg1-Ps87	Cg5-Pg1-Ps88
	Cg5-Pg1-Ps89	Cg5-Pg1-Ps90	Cg5-Pg1-Ps91	Cg5-Pg1-Ps92
30	Cg5-Pg1-Ps93	Cg5-Pg1-Ps94	Cg5-Pg1-Ps95	Cg5-Pg1-Ps96
	Cg5-Pg1-Ps97	Cg5-Pg1-Ps98	Cg5-Pg1-Ps99	Cg5-Pg1-Ps100
	Cg5-Pg1-Ps101	Cg5-Pg1-Ps102	Cg5-Pg1-Ps103	Cg5-Pg1-Ps104
	Cg5-Pg1-Ps105	Cg5-Pg1-Ps106	Cg5-Pg1-Ps107	Cg5-Pg1-Ps108
	Cg5-Pg1-Ps109	Cg5-Pg1-Ps110	Cg5-Pg1-Ps111	Cg5-Pg1-Ps112
35	Cg5-Pg1-Ps113	Cg5-Pg1-Ps114	Cg5-Pg1-Ps115	Cg5-Pg1-Ps116
	Cg5-Pg1-Ps117	Cg5-Pg1-Ps118	Cg5-Pg1-Ps119	Cg5-Pg1-Ps120

	Cg5-Pg1-Ps121	Cg5-Pg1-Ps122	Cg5-Pg1-Ps123	Cg5-Pg1-Ps124
	Cg5-Pg1-Ps125	Cg5-Pg1-Ps126	Cg5-Pg1-Ps127	Cg5-Pg1-Ps128
	Cg5-Pg1-Ps129	Cg5-Pg1-Ps130	Cg5-Pg1-Ps131	Cg5-Pg1-Ps132
	Cg5-Pg1-Ps133	Cg5-Pg1-Ps134	Cg5-Pg1-Ps135	Cg5-Pg1-Ps136
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	Cg5-Pg1-Ps141	Cg5-Pg1-Ps142	Cg5-Pg1-Ps143	Cg5-Pg1-Ps144
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	Cgl8-Pgl-Ps125	Cgl8-Pgl-Ps126	Cgl8-Pgl-Ps127	Cgl8-Pgl-Ps128
	Cgl8-Pgl-Ps129	Cgl8-Pgl-Ps130	Cgl8-Pgl-Ps131	Cgl8-Pgl-Ps132
35	Cgl8-Pgl-Ps133	Cgl8-Pgl-Ps134	Cgl8-Pgl-Ps135	Cgl8-Pgl-Ps136
	Cgl8-Pgl-Ps137	Cgl8-Pgl-Ps138	Cgl8-Pgl-Ps139	Cgl8-Pgl-Ps140
	Cgl8-Pgl-Ps141	Cgl8-Pgl-Ps142	Cgl8-Pgl-Ps143	Cgl8-Pgl-Ps144
	Cgl8-Pgl-Ps145	Cgl8-Pgl-Ps146	Cgl8-Pgl-Ps147	Cgl8-Pgl-Ps148
	Cgl8-Pgl-Ps149	Cgl8-Pgl-Ps150	Cgl8-Pgl-Ps151	Cgl8-Pgl-Ps152
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	Cgl8-Pgl-Ps157	Cgl8-Pgl-Ps158	Cgl8-Pgl-Ps159	Cgl8-Pgl-Ps160
	Cgl8-Pgl-Ps161	Cgl8-Pgl-Ps162	Cgl8-Pgl-Ps163	Cgl8-Pgl-Ps164
	Cgl8-Pgl-Ps165	Cgl8-Pgl-Ps166	Cgl8-Pgl-Ps167	Cgl8-Pgl-Ps168
	Cgl8-Pgl-Ps169	Cgl8-Pgl-Ps170	Cgl8-Pgl-Ps171	Cgl8-Pgl-Ps172
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	Cgl8-Pgl-Ps177	Cgl8-Pgl-Ps178	Cgl8-Pgl-Ps179	Cgl8-Pgl-Ps180
	Cgl8-Pgl-Ps181	Cgl8-Pgl-Ps182	Cgl8-Pgl-Ps183	Cgl8-Pgl-Ps184
	Cgl8-Pgl-Ps185	Cgl8-Pgl-Ps186	Cgl8-Pgl-Ps187	Cgl8-Pgl-Ps188
	Cgl8-Pgl-Ps189	Cgl8-Pgl-Ps190	Cgl8-Pgl-Ps191	Cgl8-Pgl-Ps192
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	Cgl8-Pgl-Ps197	Cgl8-Pgl-Ps198	Cgl8-Pgl-Ps199	Cgl8-Pgl-Ps200
	Cgl8-Pgl-Ps201	Cgl8-Pgl-Ps202	Cgl8-Pgl-Ps203	Cgl8-Pgl-Ps204

-50-

	Cg18-Pg1-Ps205	Cg18-Pg1-Ps206	Cg18-Pg1-Ps207	Cg18-Pg1-Ps208
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	Cg18-Pg1-Ps213	Cg18-Pg1-Ps214	Cg18-Pg1-Ps215	Cg18-Pg1-Ps216
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	Cg18-Pg1-Ps225	Cg18-Pg1-Ps226	Cg18-Pg1-Ps227	Cg18-Pg1-Ps228
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	Cg21-Pg1-Ps1	Cg21-Pg1-Ps2	Cg21-Pg1-Ps3	Cg21-Pg1-Ps4
	Cg21-Pg1-Ps5	Cg21-Pg1-Ps6	Cg21-Pg1-Ps7	Cg21-Pg1-Ps8
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	Cg21-Pg1-Ps17	Cg21-Pg1-Ps18	Cg21-Pg1-Ps19	Cg21-Pg1-Ps20
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	Cg21-Pg1-Ps25	Cg21-Pg1-Ps26	Cg21-Pg1-Ps27	Cg21-Pg1-Ps28
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	Cg21-Pg1-Ps37	Cg21-Pg1-Ps38	Cg21-Pg1-Ps39	Cg21-Pg1-Ps40
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	Cg21-Pg1-Ps45	Cg21-Pg1-Ps46	Cg21-Pg1-Ps47	Cg21-Pg1-Ps48
	Cg21-Pg1-Ps49	Cg21-Pg1-Ps50	Cg21-Pg1-Ps51	Cg21-Pg1-Ps52
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	Cg21-Pg1-Ps57	Cg21-Pg1-Ps58	Cg21-Pg1-Ps59	Cg21-Pg1-Ps60
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	Cg21-Pg1-Ps65	Cg21-Pg1-Ps66	Cg21-Pg1-Ps67	Cg21-Pg1-Ps68
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	Cg21-Pg1-Ps89	Cg21-Pg1-Ps90	Cg21-Pg1-Ps91	Cg21-Pg1-Ps92
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	Cg21-Pg1-Ps117	Cg21-Pg1-Ps118	Cg21-Pg1-Ps119	Cg21-Pg1-Ps120
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	Cg21-Pg1-Ps149	Cg21-Pg1-Ps150	Cg21-Pg1-Ps151	Cg21-Pg1-Ps152
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	Cg21-Pg1-Ps157	Cg21-Pg1-Ps158	Cg21-Pg1-Ps159	Cg21-Pg1-Ps160
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	Cg21-Pg1-Ps173	Cg21-Pg1-Ps174	Cg21-Pg1-Ps175	Cg21-Pg1-Ps176
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	Cg21-Pg1-Ps213	Cg21-Pg1-Ps214	Cg21-Pg1-Ps215	Cg21-Pg1-Ps216
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15	Cg21-Pg1-Ps221	Cg21-Pg1-Ps222	Cg21-Pg1-Ps223	Cg21-Pg1-Ps224
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	Cg22-Pg1-Ps45	Cg22-Pg1-Ps46	Cg22-Pg1-Ps47	Cg22-Pg1-Ps48
	Cg22-Pg1-Ps49	Cg22-Pg1-Ps50	Cg22-Pg1-Ps51	Cg22-Pg1-Ps52
35	Cg22-Pg1-Ps53	Cg22-Pg1-Ps54	Cg22-Pg1-Ps55	Cg22-Pg1-Ps56
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	Cg22-Pg1-Ps105	Cg22-Pg1-Ps106	Cg22-Pg1-Ps107	Cg22-Pg1-Ps108
	Cg22-Pg1-Ps109	Cg22-Pg1-Ps110	Cg22-Pg1-Ps111	Cg22-Pg1-Ps112
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	Cg22-Pg1-Ps117	Cg22-Pg1-Ps118	Cg22-Pg1-Ps119	Cg22-Pg1-Ps120
	Cg22-Pg1-Ps121	Cg22-Pg1-Ps122	Cg22-Pg1-Ps123	Cg22-Pg1-Ps124

-52-

	Cg22-Pg1-Ps125	Cg22-Pg1-Ps126	Cg22-Pg1-Ps127	Cg22-Pg1-Ps128
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	Cg23-Pg1-Ps93	Cg23-Pg1-Ps94	Cg23-Pg1-Ps95	Cg23-Pg1-Ps96
	Cg23-Pg1-Ps97	Cg23-Pg1-Ps98	Cg23-Pg1-Ps99	Cg23-Pg1-Ps100
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	Cg23-Pg1-Ps105	Cg23-Pg1-Ps106	Cg23-Pg1-Ps107	Cg23-Pg1-Ps108
	Cg23-Pg1-Ps109	Cg23-Pg1-Ps110	Cg23-Pg1-Ps111	Cg23-Pg1-Ps112
	Cg23-Pg1-Ps113	Cg23-Pg1-Ps114	Cg23-Pg1-Ps115	Cg23-Pg1-Ps116
	Cg23-Pg1-Ps117	Cg23-Pg1-Ps118	Cg23-Pg1-Ps119	Cg23-Pg1-Ps120
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	Cg23-Pg1-Ps125	Cg23-Pg1-Ps126	Cg23-Pg1-Ps127	Cg23-Pg1-Ps128
	Cg23-Pg1-Ps129	Cg23-Pg1-Ps130	Cg23-Pg1-Ps131	Cg23-Pg1-Ps132
	Cg23-Pg1-Ps133	Cg23-Pg1-Ps134	Cg23-Pg1-Ps135	Cg23-Pg1-Ps136
	Cg23-Pg1-Ps137	Cg23-Pg1-Ps138	Cg23-Pg1-Ps139	Cg23-Pg1-Ps140
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	Cg23-Pg1-Ps145	Cg23-Pg1-Ps146	Cg23-Pg1-Ps147	Cg23-Pg1-Ps148
	Cg23-Pg1-Ps149	Cg23-Pg1-Ps150	Cg23-Pg1-Ps151	Cg23-Pg1-Ps152
	Cg23-Pg1-Ps153	Cg23-Pg1-Ps154	Cg23-Pg1-Ps155	Cg23-Pg1-Ps156
	Cg23-Pg1-Ps157	Cg23-Pg1-Ps158	Cg23-Pg1-Ps159	Cg23-Pg1-Ps160
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	Cg23-Pg1-Ps165	Cg23-Pg1-Ps166	Cg23-Pg1-Ps167	Cg23-Pg1-Ps168
	Cg23-Pg1-Ps169	Cg23-Pg1-Ps170	Cg23-Pg1-Ps171	Cg23-Pg1-Ps172
	Cg23-Pg1-Ps173	Cg23-Pg1-Ps174	Cg23-Pg1-Ps175	Cg23-Pg1-Ps176
	Cg23-Pg1-Ps177	Cg23-Pg1-Ps178	Cg23-Pg1-Ps179	Cg23-Pg1-Ps180
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	Cg23-Pg1-Ps185	Cg23-Pg1-Ps186	Cg23-Pg1-Ps187	Cg23-Pg1-Ps188
	Cg23-Pg1-Ps189	Cg23-Pg1-Ps190	Cg23-Pg1-Ps191	Cg23-Pg1-Ps192
	Cg23-Pg1-Ps193	Cg23-Pg1-Ps194	Cg23-Pg1-Ps195	Cg23-Pg1-Ps196
	Cg23-Pg1-Ps197	Cg23-Pg1-Ps198	Cg23-Pg1-Ps199	Cg23-Pg1-Ps200
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	Cg23-Pg1-Ps205	Cg23-Pg1-Ps206	Cg23-Pg1-Ps207	Cg23-Pg1-Ps208
	Cg23-Pg1-Ps209	Cg23-Pg1-Ps210	Cg23-Pg1-Ps211	Cg23-Pg1-Ps212
	Cg23-Pg1-Ps213	Cg23-Pg1-Ps214	Cg23-Pg1-Ps215	Cg23-Pg1-Ps216
	Cg23-Pg1-Ps217	Cg23-Pg1-Ps218	Cg23-Pg1-Ps219	Cg23-Pg1-Ps220
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	Cg23-Pg1-Ps225	Cg23-Pg1-Ps226	Cg23-Pg1-Ps227	Cg23-Pg1-Ps228
	Cg23-Pg1-Ps229	Cg23-Pg1-Ps230	Cg23-Pg1-Ps231	Cg23-Pg1-Ps232
	Cg23-Pg1-Ps233	Cg23-Pg1-Ps234	Cg23-Pg1-Ps235	Cg23-Pg1-Ps236
	Cg23-Pg1-Ps237	Cg23-Pg1-Ps238	Cg23-Pg1-Ps239	Cg23-Pg1-Ps240
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	Cg24-Pg1-Ps5	Cg24-Pg1-Ps6	Cg24-Pg1-Ps7	Cg24-Pg1-Ps8
	Cg24-Pg1-Ps9	Cg24-Pg1-Ps10	Cg24-Pg1-Ps11	Cg24-Pg1-Ps12
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	Cg24-Pg1-Ps17	Cg24-Pg1-Ps18	Cg24-Pg1-Ps19	Cg24-Pg1-Ps20
	Cg24-Pg1-Ps21	Cg24-Pg1-Ps22	Cg24-Pg1-Ps23	Cg24-Pg1-Ps24
	Cg24-Pg1-Ps25	Cg24-Pg1-Ps26	Cg24-Pg1-Ps27	Cg24-Pg1-Ps28
	Cg24-Pg1-Ps29	Cg24-Pg1-Ps30	Cg24-Pg1-Ps31	Cg24-Pg1-Ps32
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	Cg24-Pg1-Ps37	Cg24-Pg1-Ps38	Cg24-Pg1-Ps39	Cg24-Pg1-Ps40
	Cg24-Pg1-Ps41	Cg24-Pg1-Ps42	Cg24-Pg1-Ps43	Cg24-Pg1-Ps44

-54-

	Cg24-Pgl-Ps45	Cg24-Pgl-Ps46	Cg24-Pgl-Ps47	Cg24-Pgl-Ps48
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	Cg24-Pgl-Ps57	Cg24-Pgl-Ps58	Cg24-Pgl-Ps59	Cg24-Pgl-Ps60
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	Cg24-Pgl-Ps233	Cg24-Pgl-Ps234	Cg24-Pgl-Ps235	Cg24-Pgl-Ps236
	Cg24-Pgl-Ps237	Cg24-Pgl-Ps238	Cg24-Pgl-Ps239	Cg24-Pgl-Ps240
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	Cg25-Pgl-Ps1	Cg25-Pgl-Ps2	Cg25-Pgl-Ps3	Cg25-Pgl-Ps4

-55-

	Cg25-Pg1-Ps5	Cg25-Pg1-Ps6	Cg25-Pg1-Ps7	Cg25-Pg1-Ps8
	Cg25-Pg1-Ps9	Cg25-Pg1-Ps10	Cg25-Pg1-Ps11	Cg25-Pg1-Ps12
	Cg25-Pg1-Ps13	Cg25-Pg1-Ps14	Cg25-Pg1-Ps15	Cg25-Pg1-Ps16
	Cg25-Pg1-Ps17	Cg25-Pg1-Ps18	Cg25-Pg1-Ps19	Cg25-Pg1-Ps20
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	Cg25-Pg1-Ps169	Cg25-Pg1-Ps170	Cg25-Pg1-Ps171	Cg25-Pg1-Ps172
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	Cg25-Pg1-Ps197	Cg25-Pg1-Ps198	Cg25-Pg1-Ps199	Cg25-Pg1-Ps200
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	Cg25-Pg1-Ps205	Cg25-Pg1-Ps206	Cg25-Pg1-Ps207	Cg25-Pg1-Ps208
	Cg25-Pg1-Ps209	Cg25-Pg1-Ps210	Cg25-Pg1-Ps211	Cg25-Pg1-Ps212

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	Cg26-Pg1-Ps53	Cg26-Pg1-Ps54	Cg26-Pg1-Ps55	Cg26-Pg1-Ps56
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	Cg26-Pg1-Ps77	Cg26-Pg1-Ps78	Cg26-Pg1-Ps79	Cg26-Pg1-Ps80
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	Cg26-Pg1-Ps85	Cg26-Pg1-Ps86	Cg26-Pg1-Ps87	Cg26-Pg1-Ps88
	Cg26-Pg1-Ps89	Cg26-Pg1-Ps90	Cg26-Pg1-Ps91	Cg26-Pg1-Ps92
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	Cg26-Pg1-Ps121	Cg26-Pg1-Ps122	Cg26-Pg1-Ps123	Cg26-Pg1-Ps124
	Cg26-Pg1-Ps125	Cg26-Pg1-Ps126	Cg26-Pg1-Ps127	Cg26-Pg1-Ps128
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	Cg26-Pg1-Ps137	Cg26-Pg1-Ps138	Cg26-Pg1-Ps139	Cg26-Pg1-Ps140
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55	Cg26-Pg1-Ps145	Cg26-Pg1-Ps146	Cg26-Pg1-Ps147	Cg26-Pg1-Ps148
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-58-

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	Cg29-Pg1-Ps77	Cg29-Pg1-Ps78	Cg29-Pg1-Ps79	Cg29-Pg1-Ps80
	Cg29-Pg1-Ps81	Cg29-Pg1-Ps82	Cg29-Pg1-Ps83	Cg29-Pg1-Ps84
	Cg29-Pg1-Ps85	Cg29-Pg1-Ps86	Cg29-Pg1-Ps87	Cg29-Pg1-Ps88
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	Cg29-Pg1-Ps93	Cg29-Pg1-Ps94	Cg29-Pg1-Ps95	Cg29-Pg1-Ps96
	Cg29-Pg1-Ps97	Cg29-Pg1-Ps98	Cg29-Pg1-Ps99	Cg29-Pg1-Ps100
	Cg29-Pg1-Ps101	Cg29-Pg1-Ps102	Cg29-Pg1-Ps103	Cg29-Pg1-Ps104
	Cg29-Pg1-Ps105	Cg29-Pg1-Ps106	Cg29-Pg1-Ps107	Cg29-Pg1-Ps108
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	Cg29-Pg1-Ps113	Cg29-Pg1-Ps114	Cg29-Pg1-Ps115	Cg29-Pg1-Ps116
	Cg29-Pg1-Ps117	Cg29-Pg1-Ps118	Cg29-Pg1-Ps119	Cg29-Pg1-Ps120
	Cg29-Pg1-Ps121	Cg29-Pg1-Ps122	Cg29-Pg1-Ps123	Cg29-Pg1-Ps124
	Cg29-Pg1-Ps125	Cg29-Pg1-Ps126	Cg29-Pg1-Ps127	Cg29-Pg1-Ps128
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	Cg30-Pg1-Ps5	Cg30-Pg1-Ps6	Cg30-Pg1-Ps7	Cg30-Pg1-Ps8
	Cg30-Pg1-Ps9	Cg30-Pg1-Ps10	Cg30-Pg1-Ps11	Cg30-Pg1-Ps12

	Cg30-Pg1-Ps13	Cg30-Pg1-Ps14	Cg30-Pg1-Ps15	Cg30-Pg1-Ps16
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	Cg30-Pg1-Ps213	Cg30-Pg1-Ps214	Cg30-Pg1-Ps215	Cg30-Pg1-Ps216
	Cg30-Pg1-Ps217	Cg30-Pg1-Ps218	Cg30-Pg1-Ps219	Cg30-Pg1-Ps220

-62-

5	Cg30-Pg1-Ps221	Cg30-Pg1-Ps222	Cg30-Pg1-Ps223	Cg30-Pg1-Ps224
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	Cg31-Pg1-Ps45	Cg31-Pg1-Ps46	Cg31-Pg1-Ps47	Cg31-Pg1-Ps48
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	Cg31-Pg1-Ps173	Cg31-Pg1-Ps174	Cg31-Pg1-Ps175	Cg31-Pg1-Ps176
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	Cg32-Pg1-Ps5	Cg32-Pg1-Ps6	Cg32-Pg1-Ps7	Cg32-Pg1-Ps8
	Cg32-Pg1-Ps9	Cg32-Pg1-Ps10	Cg32-Pg1-Ps11	Cg32-Pg1-Ps12
	Cg32-Pg1-Ps13	Cg32-Pg1-Ps14	Cg32-Pg1-Ps15	Cg32-Pg1-Ps16
	Cg32-Pg1-Ps17	Cg32-Pg1-Ps18	Cg32-Pg1-Ps19	Cg32-Pg1-Ps20
25	Cg32-Pg1-Ps21	Cg32-Pg1-Ps22	Cg32-Pg1-Ps23	Cg32-Pg1-Ps24
	Cg32-Pg1-Ps25	Cg32-Pg1-Ps26	Cg32-Pg1-Ps27	Cg32-Pg1-Ps28
	Cg32-Pg1-Ps29	Cg32-Pg1-Ps30	Cg32-Pg1-Ps31	Cg32-Pg1-Ps32
	Cg32-Pg1-Ps33	Cg32-Pg1-Ps34	Cg32-Pg1-Ps35	Cg32-Pg1-Ps36
	Cg32-Pg1-Ps37	Cg32-Pg1-Ps38	Cg32-Pg1-Ps39	Cg32-Pg1-Ps40
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	Cg32-Pg1-Ps45	Cg32-Pg1-Ps46	Cg32-Pg1-Ps47	Cg32-Pg1-Ps48
	Cg32-Pg1-Ps49	Cg32-Pg1-Ps50	Cg32-Pg1-Ps51	Cg32-Pg1-Ps52
	Cg32-Pg1-Ps53	Cg32-Pg1-Ps54	Cg32-Pg1-Ps55	Cg32-Pg1-Ps56
	Cg32-Pg1-Ps57	Cg32-Pg1-Ps58	Cg32-Pg1-Ps59	Cg32-Pg1-Ps60
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	Cg32-Pg1-Ps69	Cg32-Pg1-Ps70	Cg32-Pg1-Ps71	Cg32-Pg1-Ps72
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	Cg32-Pg1-Ps77	Cg32-Pg1-Ps78	Cg32-Pg1-Ps79	Cg32-Pg1-Ps80
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	Cg32-Pg1-Ps89	Cg32-Pg1-Ps90	Cg32-Pg1-Ps91	Cg32-Pg1-Ps92
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	Cg32-Pg1-Ps97	Cg32-Pg1-Ps98	Cg32-Pg1-Ps99	Cg32-Pg1-Ps100
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	Cg32-Pg1-Ps109	Cg32-Pg1-Ps110	Cg32-Pg1-Ps111	Cg32-Pg1-Ps112
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	Cg32-Pg1-Ps125	Cg32-Pg1-Ps126	Cg32-Pg1-Ps127	Cg32-Pg1-Ps128
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	Cg32-Pg1-Ps137	Cg32-Pg1-Ps138	Cg32-Pg1-Ps139	Cg32-Pg1-Ps140

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	Cg38-Pgl-Ps17	Cg38-Pgl-Ps18	Cg38-Pgl-Ps19	Cg38-Pgl-Ps20

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	Cg38-Pg1-Ps29	Cg38-Pg1-Ps30	Cg38-Pg1-Ps31	Cg38-Pg1-Ps32
	Cg38-Pg1-Ps33	Cg38-Pg1-Ps34	Cg38-Pg1-Ps35	Cg38-Pg1-Ps36
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	Cg38-Pg1-Ps41	Cg38-Pg1-Ps42	Cg38-Pg1-Ps43	Cg38-Pg1-Ps44
	Cg38-Pg1-Ps45	Cg38-Pg1-Ps46	Cg38-Pg1-Ps47	Cg38-Pg1-Ps48
	Cg38-Pg1-Ps49	Cg38-Pg1-Ps50	Cg38-Pg1-Ps51	Cg38-Pg1-Ps52
	Cg38-Pg1-Ps53	Cg38-Pg1-Ps54	Cg38-Pg1-Ps55	Cg38-Pg1-Ps56
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	Cg38-Pg1-Ps61	Cg38-Pg1-Ps62	Cg38-Pg1-Ps63	Cg38-Pg1-Ps64
	Cg38-Pg1-Ps65	Cg38-Pg1-Ps66	Cg38-Pg1-Ps67	Cg38-Pg1-Ps68
	Cg38-Pg1-Ps69	Cg38-Pg1-Ps70	Cg38-Pg1-Ps71	Cg38-Pg1-Ps72
	Cg38-Pg1-Ps73	Cg38-Pg1-Ps74	Cg38-Pg1-Ps75	Cg38-Pg1-Ps76
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	Cg38-Pg1-Ps81	Cg38-Pg1-Ps82	Cg38-Pg1-Ps83	Cg38-Pg1-Ps84
	Cg38-Pg1-Ps85	Cg38-Pg1-Ps86	Cg38-Pg1-Ps87	Cg38-Pg1-Ps88
	Cg38-Pg1-Ps89	Cg38-Pg1-Ps90	Cg38-Pg1-Ps91	Cg38-Pg1-Ps92
	Cg38-Pg1-Ps93	Cg38-Pg1-Ps94	Cg38-Pg1-Ps95	Cg38-Pg1-Ps96
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	Cg38-Pg1-Ps105	Cg38-Pg1-Ps106	Cg38-Pg1-Ps107	Cg38-Pg1-Ps108
	Cg38-Pg1-Ps109	Cg38-Pg1-Ps110	Cg38-Pg1-Ps111	Cg38-Pg1-Ps112
	Cg38-Pg1-Ps113	Cg38-Pg1-Ps114	Cg38-Pg1-Ps115	Cg38-Pg1-Ps116
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	Cg38-Pg1-Ps125	Cg38-Pg1-Ps126	Cg38-Pg1-Ps127	Cg38-Pg1-Ps128
	Cg38-Pg1-Ps129	Cg38-Pg1-Ps130	Cg38-Pg1-Ps131	Cg38-Pg1-Ps132
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	Cg38-Pg1-Ps145	Cg38-Pg1-Ps146	Cg38-Pg1-Ps147	Cg38-Pg1-Ps148
	Cg38-Pg1-Ps149	Cg38-Pg1-Ps150	Cg38-Pg1-Ps151	Cg38-Pg1-Ps152
	Cg38-Pg1-Ps153	Cg38-Pg1-Ps154	Cg38-Pg1-Ps155	Cg38-Pg1-Ps156
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	Cg38-Pg1-Ps185	Cg38-Pg1-Ps186	Cg38-Pg1-Ps187	Cg38-Pg1-Ps188
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	Cg38-Pg1-Ps225	Cg38-Pg1-Ps226	Cg38-Pg1-Ps227	Cg38-Pg1-Ps228

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	Cg38-Pg1-Ps237	Cg38-Pg1-Ps238	Cg38-Pg1-Ps239	Cg38-Pg1-Ps240
	Cg38-Pg1-Ps241	Cg38-Pg1-Ps242	Cg38-Pg1-Ps243	
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	Cg39-Pg1-Ps185	Cg39-Pg1-Ps186	Cg39-Pg1-Ps187	Cg39-Pg1-Ps188

	Cg39-Pgl-Ps189	Cg39-Pgl-Ps190	Cg39-Pgl-Ps191	Cg39-Pgl-Ps192
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	Cg39-Pgl-Ps237	Cg39-Pgl-Ps238	Cg39-Pgl-Ps239	Cg39-Pgl-Ps240
	Cg39-Pgl-Ps241	Cg39-Pgl-Ps242	Cg39-Pgl-Ps243	
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	Cg41-Pgl-Ps5	Cg41-Pgl-Ps6	Cg41-Pgl-Ps7	Cg41-Pgl-Ps8
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	Cg41-Pgl-Ps141	Cg41-Pgl-Ps142	Cg41-Pgl-Ps143	Cg41-Pgl-Ps144
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	Cg41-Pg1-Ps237	Cg41-Pg1-Ps238	Cg41-Pg1-Ps239	Cg41-Pg1-Ps240
	Cg41-Pg1-Ps241	Cg41-Pg1-Ps242	Cg41-Pg1-Ps243	
25	Cg42-Pg1-Ps1	Cg42-Pg1-Ps2	Cg42-Pg1-Ps3	Cg42-Pg1-Ps4
	Cg42-Pg1-Ps5	Cg42-Pg1-Ps6	Cg42-Pg1-Ps7	Cg42-Pg1-Ps8
	Cg42-Pg1-Ps9	Cg42-Pg1-Ps10	Cg42-Pg1-Ps11	Cg42-Pg1-Ps12
	Cg42-Pg1-Ps13	Cg42-Pg1-Ps14	Cg42-Pg1-Ps15	Cg42-Pg1-Ps16
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	Cg42-Pg1-Ps21	Cg42-Pg1-Ps22	Cg42-Pg1-Ps23	Cg42-Pg1-Ps24
	Cg42-Pg1-Ps25	Cg42-Pg1-Ps26	Cg42-Pg1-Ps27	Cg42-Pg1-Ps28
	Cg42-Pg1-Ps29	Cg42-Pg1-Ps30	Cg42-Pg1-Ps31	Cg42-Pg1-Ps32
	Cg42-Pg1-Ps33	Cg42-Pg1-Ps34	Cg42-Pg1-Ps35	Cg42-Pg1-Ps36
35	Cg42-Pg1-Ps37	Cg42-Pg1-Ps38	Cg42-Pg1-Ps39	Cg42-Pg1-Ps40
	Cg42-Pg1-Ps41	Cg42-Pg1-Ps42	Cg42-Pg1-Ps43	Cg42-Pg1-Ps44
	Cg42-Pg1-Ps45	Cg42-Pg1-Ps46	Cg42-Pg1-Ps47	Cg42-Pg1-Ps48
	Cg42-Pg1-Ps49	Cg42-Pg1-Ps50	Cg42-Pg1-Ps51	Cg42-Pg1-Ps52
	Cg42-Pg1-Ps53	Cg42-Pg1-Ps54	Cg42-Pg1-Ps55	Cg42-Pg1-Ps56
40	Cg42-Pg1-Ps57	Cg42-Pg1-Ps58	Cg42-Pg1-Ps59	Cg42-Pg1-Ps60
	Cg42-Pg1-Ps61	Cg42-Pg1-Ps62	Cg42-Pg1-Ps63	Cg42-Pg1-Ps64
	Cg42-Pg1-Ps65	Cg42-Pg1-Ps66	Cg42-Pg1-Ps67	Cg42-Pg1-Ps68
	Cg42-Pg1-Ps69	Cg42-Pg1-Ps70	Cg42-Pg1-Ps71	Cg42-Pg1-Ps72
	Cg42-Pg1-Ps73	Cg42-Pg1-Ps74	Cg42-Pg1-Ps75	Cg42-Pg1-Ps76
45	Cg42-Pg1-Ps77	Cg42-Pg1-Ps78	Cg42-Pg1-Ps79	Cg42-Pg1-Ps80
	Cg42-Pg1-Ps81	Cg42-Pg1-Ps82	Cg42-Pg1-Ps83	Cg42-Pg1-Ps84
	Cg42-Pg1-Ps85	Cg42-Pg1-Ps86	Cg42-Pg1-Ps87	Cg42-Pg1-Ps88
	Cg42-Pg1-Ps89	Cg42-Pg1-Ps90	Cg42-Pg1-Ps91	Cg42-Pg1-Ps92
	Cg42-Pg1-Ps93	Cg42-Pg1-Ps94	Cg42-Pg1-Ps95	Cg42-Pg1-Ps96
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	Cg42-Pg1-Ps101	Cg42-Pg1-Ps102	Cg42-Pg1-Ps103	Cg42-Pg1-Ps104
	Cg42-Pg1-Ps105	Cg42-Pg1-Ps106	Cg42-Pg1-Ps107	Cg42-Pg1-Ps108

	Cg42-Pgl-Ps109	Cg42-Pgl-Ps110	Cg42-Pgl-Ps111	Cg42-Pgl-Ps112
	Cg42-Pgl-Ps113	Cg42-Pgl-Ps114	Cg42-Pgl-Ps115	Cg42-Pgl-Ps116
	Cg42-Pgl-Ps117	Cg42-Pgl-Ps118	Cg42-Pgl-Ps119	Cg42-Pgl-Ps120
	Cg42-Pgl-Ps121	Cg42-Pgl-Ps122	Cg42-Pgl-Ps123	Cg42-Pgl-Ps124
5	Cg42-Pgl-Ps125	Cg42-Pgl-Ps126	Cg42-Pgl-Ps127	Cg42-Pgl-Ps128
	Cg42-Pgl-Ps129	Cg42-Pgl-Ps130	Cg42-Pgl-Ps131	Cg42-Pgl-Ps132
	Cg42-Pgl-Ps133	Cg42-Pgl-Ps134	Cg42-Pgl-Ps135	Cg42-Pgl-Ps136
	Cg42-Pgl-Ps137	Cg42-Pgl-Ps138	Cg42-Pgl-Ps139	Cg42-Pgl-Ps140
	Cg42-Pgl-Ps141	Cg42-Pgl-Ps142	Cg42-Pgl-Ps143	Cg42-Pgl-Ps144
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	Cg42-Pgl-Ps149	Cg42-Pgl-Ps150	Cg42-Pgl-Ps151	Cg42-Pgl-Ps152
	Cg42-Pgl-Ps153	Cg42-Pgl-Ps154	Cg42-Pgl-Ps155	Cg42-Pgl-Ps156
	Cg42-Pgl-Ps157	Cg42-Pgl-Ps158	Cg42-Pgl-Ps159	Cg42-Pgl-Ps160
	Cg42-Pgl-Ps161	Cg42-Pgl-Ps162	Cg42-Pgl-Ps163	Cg42-Pgl-Ps164
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	Cg42-Pgl-Ps169	Cg42-Pgl-Ps170	Cg42-Pgl-Ps171	Cg42-Pgl-Ps172
	Cg42-Pgl-Ps173	Cg42-Pgl-Ps174	Cg42-Pgl-Ps175	Cg42-Pgl-Ps176
	Cg42-Pgl-Ps177	Cg42-Pgl-Ps178	Cg42-Pgl-Ps179	Cg42-Pgl-Ps180
	Cg42-Pgl-Ps181	Cg42-Pgl-Ps182	Cg42-Pgl-Ps183	Cg42-Pgl-Ps184
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	Cg42-Pgl-Ps189	Cg42-Pgl-Ps190	Cg42-Pgl-Ps191	Cg42-Pgl-Ps192
	Cg42-Pgl-Ps193	Cg42-Pgl-Ps194	Cg42-Pgl-Ps195	Cg42-Pgl-Ps196
	Cg42-Pgl-Ps197	Cg42-Pgl-Ps198	Cg42-Pgl-Ps199	Cg42-Pgl-Ps200
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	Cg42-Pgl-Ps213	Cg42-Pgl-Ps214	Cg42-Pgl-Ps215	Cg42-Pgl-Ps216
	Cg42-Pgl-Ps217	Cg42-Pgl-Ps218	Cg42-Pgl-Ps219	Cg42-Pgl-Ps220
	Cg42-Pgl-Ps221	Cg42-Pgl-Ps222	Cg42-Pgl-Ps223	Cg42-Pgl-Ps224
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	Cg42-Pgl-Ps229	Cg42-Pgl-Ps230	Cg42-Pgl-Ps231	Cg42-Pgl-Ps232
	Cg42-Pgl-Ps233	Cg42-Pgl-Ps234	Cg42-Pgl-Ps235	Cg42-Pgl-Ps236
	Cg42-Pgl-Ps237	Cg42-Pgl-Ps238	Cg42-Pgl-Ps239	Cg42-Pgl-Ps240
	Cg42-Pgl-Ps241	Cg42-Pgl-Ps242	Cg42-Pgl-Ps243	
35	Cg44-Pgl-Ps1	Cg44-Pgl-Ps2	Cg44-Pgl-Ps3	Cg44-Pgl-Ps4
	Cg44-Pgl-Ps5	Cg44-Pgl-Ps6	Cg44-Pgl-Ps7	Cg44-Pgl-Ps8
	Cg44-Pgl-Ps9	Cg44-Pgl-Ps10	Cg44-Pgl-Ps11	Cg44-Pgl-Ps12
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	Cg44-Pgl-Ps65	Cg44-Pgl-Ps66	Cg44-Pgl-Ps67	Cg44-Pgl-Ps68

-72-

	Cg44-Pgl-Ps69	Cg44-Pgl-Ps70	Cg44-Pgl-Ps71	Cg44-Pgl-Ps72
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	Cg44-Pgl-Ps241	Cg44-Pgl-Ps242	Cg44-Pgl-Ps243	
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	Cg45-Pgl-Ps25	Cg45-Pgl-Ps26	Cg45-Pgl-Ps27	Cg45-Pgl-Ps28

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	Cg45-Pg1-Ps37	Cg45-Pg1-Ps38	Cg45-Pg1-Ps39	Cg45-Pg1-Ps40
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	Cg45-Pg1-Ps153	Cg45-Pg1-Ps154	Cg45-Pg1-Ps155	Cg45-Pg1-Ps156
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	Cg45-Pg1-Ps213	Cg45-Pg1-Ps214	Cg45-Pg1-Ps215	Cg45-Pg1-Ps216
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	Cg45-Pg1-Ps229	Cg45-Pg1-Ps230	Cg45-Pg1-Ps231	Cg45-Pg1-Ps232
	Cg45-Pg1-Ps233	Cg45-Pg1-Ps234	Cg45-Pg1-Ps235	Cg45-Pg1-Ps236

-74-

	Cg45-Pgl-Ps237 Cg45-Pgl-Ps241	Cg45-Pgl-Ps238 Cg45-Pgl-Ps242	Cg45-Pgl-Ps239 Cg45-Pgl-Ps243	Cg45-Pgl-Ps240
5	Cg46-Pgl-Ps1 Cg46-Pgl-Ps5 Cg46-Pgl-Ps9 Cg46-Pgl-Ps13 Cg46-Pgl-Ps17 Cg46-Pgl-Ps21	Cg46-Pgl-Ps2 Cg46-Pgl-Ps6 Cg46-Pgl-Ps10 Cg46-Pgl-Ps14 Cg46-Pgl-Ps18 Cg46-Pgl-Ps22	Cg46-Pgl-Ps3 Cg46-Pgl-Ps7 Cg46-Pgl-Ps11 Cg46-Pgl-Ps15 Cg46-Pgl-Ps19 Cg46-Pgl-Ps23	Cg46-Pgl-Ps4 Cg46-Pgl-Ps8 Cg46-Pgl-Ps12 Cg46-Pgl-Ps16 Cg46-Pgl-Ps20 Cg46-Pgl-Ps24
10	Cg46-Pgl-Ps25 Cg46-Pgl-Ps29 Cg46-Pgl-Ps33 Cg46-Pgl-Ps37 Cg46-Pgl-Ps41	Cg46-Pgl-Ps26 Cg46-Pgl-Ps30 Cg46-Pgl-Ps34 Cg46-Pgl-Ps38 Cg46-Pgl-Ps42	Cg46-Pgl-Ps27 Cg46-Pgl-Ps31 Cg46-Pgl-Ps35 Cg46-Pgl-Ps39 Cg46-Pgl-Ps43	Cg46-Pgl-Ps28 Cg46-Pgl-Ps32 Cg46-Pgl-Ps36 Cg46-Pgl-Ps40 Cg46-Pgl-Ps44
15	Cg46-Pgl-Ps45 Cg46-Pgl-Ps49 Cg46-Pgl-Ps53 Cg46-Pgl-Ps57 Cg46-Pgl-Ps61	Cg46-Pgl-Ps46 Cg46-Pgl-Ps50 Cg46-Pgl-Ps54 Cg46-Pgl-Ps58 Cg46-Pgl-Ps62	Cg46-Pgl-Ps47 Cg46-Pgl-Ps51 Cg46-Pgl-Ps55 Cg46-Pgl-Ps59 Cg46-Pgl-Ps63	Cg46-Pgl-Ps48 Cg46-Pgl-Ps52 Cg46-Pgl-Ps56 Cg46-Pgl-Ps60 Cg46-Pgl-Ps64
20	Cg46-Pgl-Ps65 Cg46-Pgl-Ps69 Cg46-Pgl-Ps73 Cg46-Pgl-Ps77 Cg46-Pgl-Ps81	Cg46-Pgl-Ps66 Cg46-Pgl-Ps70 Cg46-Pgl-Ps74 Cg46-Pgl-Ps78 Cg46-Pgl-Ps82	Cg46-Pgl-Ps67 Cg46-Pgl-Ps71 Cg46-Pgl-Ps75 Cg46-Pgl-Ps79 Cg46-Pgl-Ps83	Cg46-Pgl-Ps68 Cg46-Pgl-Ps72 Cg46-Pgl-Ps76 Cg46-Pgl-Ps80 Cg46-Pgl-Ps84
25	Cg46-Pgl-Ps85 Cg46-Pgl-Ps89 Cg46-Pgl-Ps93 Cg46-Pgl-Ps97	Cg46-Pgl-Ps86 Cg46-Pgl-Ps90 Cg46-Pgl-Ps94 Cg46-Pgl-Ps98	Cg46-Pgl-Ps87 Cg46-Pgl-Ps91 Cg46-Pgl-Ps95 Cg46-Pgl-Ps99	Cg46-Pgl-Ps88 Cg46-Pgl-Ps92 Cg46-Pgl-Ps96 Cg46-Pgl-Ps100
30	Cg46-Pgl-Ps101 Cg46-Pgl-Ps105 Cg46-Pgl-Ps109 Cg46-Pgl-Ps113 Cg46-Pgl-Ps117	Cg46-Pgl-Ps102 Cg46-Pgl-Ps106 Cg46-Pgl-Ps110 Cg46-Pgl-Ps114 Cg46-Pgl-Ps118	Cg46-Pgl-Ps103 Cg46-Pgl-Ps107 Cg46-Pgl-Ps111 Cg46-Pgl-Ps115 Cg46-Pgl-Ps119	Cg46-Pgl-Ps104 Cg46-Pgl-Ps108 Cg46-Pgl-Ps112 Cg46-Pgl-Ps116 Cg46-Pgl-Ps120
35	Cg46-Pgl-Ps121 Cg46-Pgl-Ps125 Cg46-Pgl-Ps129 Cg46-Pgl-Ps133 Cg46-Pgl-Ps137	Cg46-Pgl-Ps122 Cg46-Pgl-Ps126 Cg46-Pgl-Ps130 Cg46-Pgl-Ps134 Cg46-Pgl-Ps138	Cg46-Pgl-Ps123 Cg46-Pgl-Ps127 Cg46-Pgl-Ps131 Cg46-Pgl-Ps135 Cg46-Pgl-Ps139	Cg46-Pgl-Ps124 Cg46-Pgl-Ps128 Cg46-Pgl-Ps132 Cg46-Pgl-Ps136 Cg46-Pgl-Ps140
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45	Cg46-Pgl-Ps161 Cg46-Pgl-Ps165 Cg46-Pgl-Ps169 Cg46-Pgl-Ps173 Cg46-Pgl-Ps177	Cg46-Pgl-Ps162 Cg46-Pgl-Ps166 Cg46-Pgl-Ps170 Cg46-Pgl-Ps174 Cg46-Pgl-Ps178	Cg46-Pgl-Ps163 Cg46-Pgl-Ps167 Cg46-Pgl-Ps171 Cg46-Pgl-Ps175 Cg46-Pgl-Ps179	Cg46-Pgl-Ps164 Cg46-Pgl-Ps168 Cg46-Pgl-Ps172 Cg46-Pgl-Ps176 Cg46-Pgl-Ps180
50	Cg46-Pgl-Ps181 Cg46-Pgl-Ps185 Cg46-Pgl-Ps189 Cg46-Pgl-Ps193	Cg46-Pgl-Ps182 Cg46-Pgl-Ps186 Cg46-Pgl-Ps190 Cg46-Pgl-Ps194	Cg46-Pgl-Ps183 Cg46-Pgl-Ps187 Cg46-Pgl-Ps191 Cg46-Pgl-Ps195	Cg46-Pgl-Ps184 Cg46-Pgl-Ps188 Cg46-Pgl-Ps192 Cg46-Pgl-Ps196

-75-

	Cg46-Pg1-Ps197	Cg46-Pg1-Ps198	Cg46-Pg1-Ps199	Cg46-Pg1-Ps200
	Cg46-Pg1-Ps201	Cg46-Pg1-Ps202	Cg46-Pg1-Ps203	Cg46-Pg1-Ps204
	Cg46-Pg1-Ps205	Cg46-Pg1-Ps206	Cg46-Pg1-Ps207	Cg46-Pg1-Ps208
	Cg46-Pg1-Ps209	Cg46-Pg1-Ps210	Cg46-Pg1-Ps211	Cg46-Pg1-Ps212
5	Cg46-Pg1-Ps213	Cg46-Pg1-Ps214	Cg46-Pg1-Ps215	Cg46-Pg1-Ps216
	Cg46-Pg1-Ps217	Cg46-Pg1-Ps218	Cg46-Pg1-Ps219	Cg46-Pg1-Ps220
	Cg46-Pg1-Ps221	Cg46-Pg1-Ps222	Cg46-Pg1-Ps223	Cg46-Pg1-Ps224
	Cg46-Pg1-Ps225	Cg46-Pg1-Ps226	Cg46-Pg1-Ps227	Cg46-Pg1-Ps228
	Cg46-Pg1-Ps229	Cg46-Pg1-Ps230	Cg46-Pg1-Ps231	Cg46-Pg1-Ps232
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	Cg46-Pg1-Ps237	Cg46-Pg1-Ps238	Cg46-Pg1-Ps239	Cg46-Pg1-Ps240
	Cg46-Pg1-Ps241	Cg46-Pg1-Ps242	Cg46-Pg1-Ps243	
	Cg47-Pg1-Ps1	Cg47-Pg1-Ps2	Cg47-Pg1-Ps3	Cg47-Pg1-Ps4
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	Cg47-Pg1-Ps9	Cg47-Pg1-Ps10	Cg47-Pg1-Ps11	Cg47-Pg1-Ps12
	Cg47-Pg1-Ps13	Cg47-Pg1-Ps14	Cg47-Pg1-Ps15	Cg47-Pg1-Ps16
	Cg47-Pg1-Ps17	Cg47-Pg1-Ps18	Cg47-Pg1-Ps19	Cg47-Pg1-Ps20
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	Cg47-Pg1-Ps33	Cg47-Pg1-Ps34	Cg47-Pg1-Ps35	Cg47-Pg1-Ps36
	Cg47-Pg1-Ps37	Cg47-Pg1-Ps38	Cg47-Pg1-Ps39	Cg47-Pg1-Ps40
	Cg47-Pg1-Ps41	Cg47-Pg1-Ps42	Cg47-Pg1-Ps43	Cg47-Pg1-Ps44
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	Cg47-Pg1-Ps49	Cg47-Pg1-Ps50	Cg47-Pg1-Ps51	Cg47-Pg1-Ps52
	Cg47-Pg1-Ps53	Cg47-Pg1-Ps54	Cg47-Pg1-Ps55	Cg47-Pg1-Ps56
	Cg47-Pg1-Ps57	Cg47-Pg1-Ps58	Cg47-Pg1-Ps59	Cg47-Pg1-Ps60
	Cg47-Pg1-Ps61	Cg47-Pg1-Ps62	Cg47-Pg1-Ps63	Cg47-Pg1-Ps64
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	Cg47-Pg1-Ps69	Cg47-Pg1-Ps70	Cg47-Pg1-Ps71	Cg47-Pg1-Ps72
	Cg47-Pg1-Ps73	Cg47-Pg1-Ps74	Cg47-Pg1-Ps75	Cg47-Pg1-Ps76
	Cg47-Pg1-Ps77	Cg47-Pg1-Ps78	Cg47-Pg1-Ps79	Cg47-Pg1-Ps80
	Cg47-Pg1-Ps81	Cg47-Pg1-Ps82	Cg47-Pg1-Ps83	Cg47-Pg1-Ps84
35	Cg47-Pg1-Ps85	Cg47-Pg1-Ps86	Cg47-Pg1-Ps87	Cg47-Pg1-Ps88
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	Cg47-Pg1-Ps129	Cg47-Pg1-Ps130	Cg47-Pg1-Ps131	Cg47-Pg1-Ps132
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50	Cg47-Pg1-Ps145	Cg47-Pg1-Ps146	Cg47-Pg1-Ps147	Cg47-Pg1-Ps148
	Cg47-Pg1-Ps149	Cg47-Pg1-Ps150	Cg47-Pg1-Ps151	Cg47-Pg1-Ps152
	Cg47-Pg1-Ps153	Cg47-Pg1-Ps154	Cg47-Pg1-Ps155	Cg47-Pg1-Ps156

-76-

	Cg47-Pgl-Ps157	Cg47-Pgl-Ps158	Cg47-Pgl-Ps159	Cg47-Pgl-Ps160
	Cg47-Pgl-Ps161	Cg47-Pgl-Ps162	Cg47-Pgl-Ps163	Cg47-Pgl-Ps164
	Cg47-Pgl-Ps165	Cg47-Pgl-Ps166	Cg47-Pgl-Ps167	Cg47-Pgl-Ps168
	Cg47-Pgl-Ps169	Cg47-Pgl-Ps170	Cg47-Pgl-Ps171	Cg47-Pgl-Ps172
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	Cg47-Pgl-Ps177	Cg47-Pgl-Ps178	Cg47-Pgl-Ps179	Cg47-Pgl-Ps180
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	Cg47-Pgl-Ps185	Cg47-Pgl-Ps186	Cg47-Pgl-Ps187	Cg47-Pgl-Ps188
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	Cg48-Pgl-Ps53	Cg48-Pgl-Ps54	Cg48-Pgl-Ps55	Cg48-Pgl-Ps56
	Cg48-Pgl-Ps57	Cg48-Pgl-Ps58	Cg48-Pgl-Ps59	Cg48-Pgl-Ps60
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	Cg48-Pgl-Ps77	Cg48-Pgl-Ps78	Cg48-Pgl-Ps79	Cg48-Pgl-Ps80
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	Cg48-Pgl-Ps109	Cg48-Pgl-Ps110	Cg48-Pgl-Ps111	Cg48-Pgl-Ps112
	Cg48-Pgl-Ps113	Cg48-Pgl-Ps114	Cg48-Pgl-Ps115	Cg48-Pgl-Ps116

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	Cg48-Pgl-Ps121	Cg48-Pgl-Ps122	Cg48-Pgl-Ps123	Cg48-Pgl-Ps124
	Cg48-Pgl-Ps125	Cg48-Pgl-Ps126	Cg48-Pgl-Ps127	Cg48-Pgl-Ps128
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	Cg48-Pgl-Ps165	Cg48-Pgl-Ps166	Cg48-Pgl-Ps167	Cg48-Pgl-Ps168
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	Cg48-Pgl-Ps193	Cg48-Pgl-Ps194	Cg48-Pgl-Ps195	Cg48-Pgl-Ps196
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	Cg49-Pgl-Ps13	Cg49-Pgl-Ps14	Cg49-Pgl-Ps15	Cg49-Pgl-Ps16
	Cg49-Pgl-Ps17	Cg49-Pgl-Ps18	Cg49-Pgl-Ps19	Cg49-Pgl-Ps20
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	Cg49-Pgl-Ps25	Cg49-Pgl-Ps26	Cg49-Pgl-Ps27	Cg49-Pgl-Ps28
	Cg49-Pgl-Ps29	Cg49-Pgl-Ps30	Cg49-Pgl-Ps31	Cg49-Pgl-Ps32
	Cg49-Pgl-Ps33	Cg49-Pgl-Ps34	Cg49-Pgl-Ps35	Cg49-Pgl-Ps36
	Cg49-Pgl-Ps37	Cg49-Pgl-Ps38	Cg49-Pgl-Ps39	Cg49-Pgl-Ps40
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	Cg49-Pgl-Ps65	Cg49-Pgl-Ps66	Cg49-Pgl-Ps67	Cg49-Pgl-Ps68
	Cg49-Pgl-Ps69	Cg49-Pgl-Ps70	Cg49-Pgl-Ps71	Cg49-Pgl-Ps72
	Cg49-Pgl-Ps73	Cg49-Pgl-Ps74	Cg49-Pgl-Ps75	Cg49-Pgl-Ps76

-78-

	Cg49-Pgl-Ps77	Cg49-Pgl-Ps78	Cg49-Pgl-Ps79	Cg49-Pgl-Ps80
	Cg49-Pgl-Ps81	Cg49-Pgl-Ps82	Cg49-Pgl-Ps83	Cg49-Pgl-Ps84
	Cg49-Pgl-Ps85	Cg49-Pgl-Ps86	Cg49-Pgl-Ps87	Cg49-Pgl-Ps88
	Cg49-Pgl-Ps89	Cg49-Pgl-Ps90	Cg49-Pgl-Ps91	Cg49-Pgl-Ps92
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	Cg50-Pgl-Ps157	Cg50-Pgl-Ps158	Cg50-Pgl-Ps159	Cg50-Pgl-Ps160
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	Cg52-Pgl-Ps49	Cg52-Pgl-Ps50	Cg52-Pgl-Ps51	Cg52-Pgl-Ps52
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	Cg52-Pgl-Ps57	Cg52-Pgl-Ps58	Cg52-Pgl-Ps59	Cg52-Pgl-Ps60
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	Cg52-Pgl-Ps65	Cg52-Pgl-Ps66	Cg52-Pgl-Ps67	Cg52-Pgl-Ps68
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	Cg52-Pgl-Ps81	Cg52-Pgl-Ps82	Cg52-Pgl-Ps83	Cg52-Pgl-Ps84
	Cg52-Pgl-Ps85	Cg52-Pgl-Ps86	Cg52-Pgl-Ps87	Cg52-Pgl-Ps88
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	Cg52-Pg1-Ps177	Cg52-Pg1-Ps178	Cg52-Pg1-Ps179	Cg52-Pg1-Ps180
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	Cg57-Pgl-Ps41	Cg57-Pgl-Ps42	Cg57-Pgl-Ps43	Cg57-Pgl-Ps44

-85-

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	Cg57-Pgl-Ps157	Cg57-Pgl-Ps158	Cg57-Pgl-Ps159	Cg57-Pgl-Ps160
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-87-

	Cg60-Pgl-Ps213	Cg60-Pgl-Ps214	Cg60-Pgl-Ps215	Cg60-Pgl-Ps216
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	Cg62-Pg1-Ps77	Cg62-Pg1-Ps78	Cg62-Pg1-Ps79	Cg62-Pg1-Ps80
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	Cg62-Pg1-Ps85	Cg62-Pg1-Ps86	Cg62-Pg1-Ps87	Cg62-Pg1-Ps88
	Cg62-Pg1-Ps89	Cg62-Pg1-Ps90	Cg62-Pg1-Ps91	Cg62-Pg1-Ps92
	Cg62-Pg1-Ps93	Cg62-Pg1-Ps94	Cg62-Pg1-Ps95	Cg62-Pg1-Ps96
	Cg62-Pg1-Ps97	Cg62-Pg1-Ps98	Cg62-Pg1-Ps99	Cg62-Pg1-Ps100
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	Cg62-Pg1-Ps105	Cg62-Pg1-Ps106	Cg62-Pg1-Ps107	Cg62-Pg1-Ps108
	Cg62-Pg1-Ps109	Cg62-Pg1-Ps110	Cg62-Pg1-Ps111	Cg62-Pg1-Ps112
	Cg62-Pg1-Ps113	Cg62-Pg1-Ps114	Cg62-Pg1-Ps115	Cg62-Pg1-Ps116
	Cg62-Pg1-Ps117	Cg62-Pg1-Ps118	Cg62-Pg1-Ps119	Cg62-Pg1-Ps120
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	Cg62-Pg1-Ps125	Cg62-Pg1-Ps126	Cg62-Pg1-Ps127	Cg62-Pg1-Ps128
	Cg62-Pg1-Ps129	Cg62-Pg1-Ps130	Cg62-Pg1-Ps131	Cg62-Pg1-Ps132

	Cg62-Pg1-Ps133	Cg62-Pg1-Ps134	Cg62-Pg1-Ps135	Cg62-Pg1-Ps136
	Cg62-Pg1-Ps137	Cg62-Pg1-Ps138	Cg62-Pg1-Ps139	Cg62-Pg1-Ps140
	Cg62-Pg1-Ps141	Cg62-Pg1-Ps142	Cg62-Pg1-Ps143	Cg62-Pg1-Ps144
	Cg62-Pg1-Ps145	Cg62-Pg1-Ps146	Cg62-Pg1-Ps147	Cg62-Pg1-Ps148
5	Cg62-Pg1-Ps149	Cg62-Pg1-Ps150	Cg62-Pg1-Ps151	Cg62-Pg1-Ps152
	Cg62-Pg1-Ps153	Cg62-Pg1-Ps154	Cg62-Pg1-Ps155	Cg62-Pg1-Ps156
	Cg62-Pg1-Ps157	Cg62-Pg1-Ps158	Cg62-Pg1-Ps159	Cg62-Pg1-Ps160
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	Cg62-Pg1-Ps165	Cg62-Pg1-Ps166	Cg62-Pg1-Ps167	Cg62-Pg1-Ps168
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	Cg62-Pg1-Ps177	Cg62-Pg1-Ps178	Cg62-Pg1-Ps179	Cg62-Pg1-Ps180
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	Cg62-Pg1-Ps185	Cg62-Pg1-Ps186	Cg62-Pg1-Ps187	Cg62-Pg1-Ps188
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	Cg62-Pg1-Ps193	Cg62-Pg1-Ps194	Cg62-Pg1-Ps195	Cg62-Pg1-Ps196
	Cg62-Pg1-Ps197	Cg62-Pg1-Ps198	Cg62-Pg1-Ps199	Cg62-Pg1-Ps200
	Cg62-Pg1-Ps201	Cg62-Pg1-Ps202	Cg62-Pg1-Ps203	Cg62-Pg1-Ps204
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	Cg62-Pg1-Ps213	Cg62-Pg1-Ps214	Cg62-Pg1-Ps215	Cg62-Pg1-Ps216
	Cg62-Pg1-Ps217	Cg62-Pg1-Ps218	Cg62-Pg1-Ps219	Cg62-Pg1-Ps220
	Cg62-Pg1-Ps221	Cg62-Pg1-Ps222	Cg62-Pg1-Ps223	Cg62-Pg1-Ps224
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	Cg62-Pg1-Ps241	Cg62-Pg1-Ps242	Cg62-Pg1-Ps243	
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	Cg63-Pg1-Ps5	Cg63-Pg1-Ps6	Cg63-Pg1-Ps7	Cg63-Pg1-Ps8
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	Cg63-Pg1-Ps17	Cg63-Pg1-Ps18	Cg63-Pg1-Ps19	Cg63-Pg1-Ps20
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	Cg63-Pg1-Ps25	Cg63-Pg1-Ps26	Cg63-Pg1-Ps27	Cg63-Pg1-Ps28
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	Cg63-Pg1-Ps45	Cg63-Pg1-Ps46	Cg63-Pg1-Ps47	Cg63-Pg1-Ps48
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	Cg63-Pg1-Ps53	Cg63-Pg1-Ps54	Cg63-Pg1-Ps55	Cg63-Pg1-Ps56
	Cg63-Pg1-Ps57	Cg63-Pg1-Ps58	Cg63-Pg1-Ps59	Cg63-Pg1-Ps60
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	Cg63-Pg1-Ps69	Cg63-Pg1-Ps70	Cg63-Pg1-Ps71	Cg63-Pg1-Ps72
	Cg63-Pg1-Ps73	Cg63-Pg1-Ps74	Cg63-Pg1-Ps75	Cg63-Pg1-Ps76
	Cg63-Pg1-Ps77	Cg63-Pg1-Ps78	Cg63-Pg1-Ps79	Cg63-Pg1-Ps80
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	Cg63-Pg1-Ps85	Cg63-Pg1-Ps86	Cg63-Pg1-Ps87	Cg63-Pg1-Ps88
	Cg63-Pg1-Ps89	Cg63-Pg1-Ps90	Cg63-Pg1-Ps91	Cg63-Pg1-Ps92

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	Cg65-Pg1-Ps45	Cg65-Pg1-Ps46	Cg65-Pg1-Ps47	Cg65-Pg1-Ps48
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	Cg65-Pg1-Ps57	Cg65-Pg1-Ps58	Cg65-Pg1-Ps59	Cg65-Pg1-Ps60
	Cg65-Pg1-Ps61	Cg65-Pg1-Ps62	Cg65-Pg1-Ps63	Cg65-Pg1-Ps64
	Cg65-Pg1-Ps65	Cg65-Pg1-Ps66	Cg65-Pg1-Ps67	Cg65-Pg1-Ps68
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	Cg65-Pg1-Ps73	Cg65-Pg1-Ps74	Cg65-Pg1-Ps75	Cg65-Pg1-Ps76
	Cg65-Pg1-Ps77	Cg65-Pg1-Ps78	Cg65-Pg1-Ps79	Cg65-Pg1-Ps80
	Cg65-Pg1-Ps81	Cg65-Pg1-Ps82	Cg65-Pg1-Ps83	Cg65-Pg1-Ps84
	Cg65-Pg1-Ps85	Cg65-Pg1-Ps86	Cg65-Pg1-Ps87	Cg65-Pg1-Ps88
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	Cg65-Pg1-Ps93	Cg65-Pg1-Ps94	Cg65-Pg1-Ps95	Cg65-Pg1-Ps96
	Cg65-Pg1-Ps97	Cg65-Pg1-Ps98	Cg65-Pg1-Ps99	Cg65-Pg1-Ps100
	Cg65-Pg1-Ps101	Cg65-Pg1-Ps102	Cg65-Pg1-Ps103	Cg65-Pg1-Ps104
	Cg65-Pg1-Ps105	Cg65-Pg1-Ps106	Cg65-Pg1-Ps107	Cg65-Pg1-Ps108
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	Cg65-Pg1-Ps113	Cg65-Pg1-Ps114	Cg65-Pg1-Ps115	Cg65-Pg1-Ps116
	Cg65-Pg1-Ps117	Cg65-Pg1-Ps118	Cg65-Pg1-Ps119	Cg65-Pg1-Ps120
	Cg65-Pg1-Ps121	Cg65-Pg1-Ps122	Cg65-Pg1-Ps123	Cg65-Pg1-Ps124
	Cg65-Pg1-Ps125	Cg65-Pg1-Ps126	Cg65-Pg1-Ps127	Cg65-Pg1-Ps128
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	Cg65-Pg1-Ps137	Cg65-Pg1-Ps138	Cg65-Pg1-Ps139	Cg65-Pg1-Ps140
	Cg65-Pg1-Ps141	Cg65-Pg1-Ps142	Cg65-Pg1-Ps143	Cg65-Pg1-Ps144
	Cg65-Pg1-Ps145	Cg65-Pg1-Ps146	Cg65-Pg1-Ps147	Cg65-Pg1-Ps148
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	Cg65-Pg1-Ps213	Cg65-Pg1-Ps214	Cg65-Pg1-Ps215	Cg65-Pg1-Ps216
	Cg65-Pg1-Ps217	Cg65-Pg1-Ps218	Cg65-Pg1-Ps219	Cg65-Pg1-Ps220

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	Cg65-Pgl-Ps237	Cg65-Pgl-Ps238	Cg65-Pgl-Ps239	Cg65-Pgl-Ps240
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	Cg67-Pgl-Ps5	Cg67-Pgl-Ps6	Cg67-Pgl-Ps7	Cg67-Pgl-Ps8
	Cg67-Pgl-Ps9	Cg67-Pgl-Ps10	Cg67-Pgl-Ps11	Cg67-Pgl-Ps12
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	Cg67-Pgl-Ps17	Cg67-Pgl-Ps18	Cg67-Pgl-Ps19	Cg67-Pgl-Ps20
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	Cg67-Pgl-Ps45	Cg67-Pgl-Ps46	Cg67-Pgl-Ps47	Cg67-Pgl-Ps48
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	Cg67-Pgl-Ps157	Cg67-Pgl-Ps158	Cg67-Pgl-Ps159	Cg67-Pgl-Ps160
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	Cg67-Pgl-Ps165	Cg67-Pgl-Ps166	Cg67-Pgl-Ps167	Cg67-Pgl-Ps168
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	Cg67-Pg1-Ps213	Cg67-Pg1-Ps214	Cg67-Pg1-Ps215	Cg67-Pg1-Ps216
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	Cg67-Pg1-Ps241	Cg67-Pg1-Ps242	Cg67-Pg1-Ps243	
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	Cg68-Pg1-Ps33	Cg68-Pg1-Ps34	Cg68-Pg1-Ps35	Cg68-Pg1-Ps36
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	Cg68-Pg1-Ps45	Cg68-Pg1-Ps46	Cg68-Pg1-Ps47	Cg68-Pg1-Ps48
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	Cg68-Pg1-Ps69	Cg68-Pg1-Ps70	Cg68-Pg1-Ps71	Cg68-Pg1-Ps72
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	Cg68-Pg1-Ps133	Cg68-Pg1-Ps134	Cg68-Pg1-Ps135	Cg68-Pg1-Ps136
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	Cg69-Pg1-Ps13	Cg69-Pg1-Ps14	Cg69-Pg1-Ps15	Cg69-Pg1-Ps16
	Cg69-Pg1-Ps17	Cg69-Pg1-Ps18	Cg69-Pg1-Ps19	Cg69-Pg1-Ps20
	Cg69-Pg1-Ps21	Cg69-Pg1-Ps22	Cg69-Pg1-Ps23	Cg69-Pg1-Ps24
	Cg69-Pg1-Ps25	Cg69-Pg1-Ps26	Cg69-Pg1-Ps27	Cg69-Pg1-Ps28
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	Cg69-Pg1-Ps37	Cg69-Pg1-Ps38	Cg69-Pg1-Ps39	Cg69-Pg1-Ps40
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	Cg69-Pg1-Ps45	Cg69-Pg1-Ps46	Cg69-Pg1-Ps47	Cg69-Pg1-Ps48
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	Cg74-Pgl-Ps73	Cg74-Pgl-Ps74	Cg74-Pgl-Ps75	Cg74-Pgl-Ps76
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	Cg74-Pgl-Ps81	Cg74-Pgl-Ps82	Cg74-Pgl-Ps83	Cg74-Pgl-Ps84
	Cg74-Pgl-Ps85	Cg74-Pgl-Ps86	Cg74-Pgl-Ps87	Cg74-Pgl-Ps88
	Cg74-Pgl-Ps89	Cg74-Pgl-Ps90	Cg74-Pgl-Ps91	Cg74-Pgl-Ps92
	Cg74-Pgl-Ps93	Cg74-Pgl-Ps94	Cg74-Pgl-Ps95	Cg74-Pgl-Ps96
30	Cg74-Pgl-Ps97	Cg74-Pgl-Ps98	Cg74-Pgl-Ps99	Cg74-Pgl-Ps100
	Cg74-Pgl-Ps101	Cg74-Pgl-Ps102	Cg74-Pgl-Ps103	Cg74-Pgl-Ps104
	Cg74-Pgl-Ps105	Cg74-Pgl-Ps106	Cg74-Pgl-Ps107	Cg74-Pgl-Ps108
	Cg74-Pgl-Ps109	Cg74-Pgl-Ps110	Cg74-Pgl-Ps111	Cg74-Pgl-Ps112
	Cg74-Pgl-Ps113	Cg74-Pgl-Ps114	Cg74-Pgl-Ps115	Cg74-Pgl-Ps116
35	Cg74-Pgl-Ps117	Cg74-Pgl-Ps118	Cg74-Pgl-Ps119	Cg74-Pgl-Ps120
	Cg74-Pgl-Ps121	Cg74-Pgl-Ps122	Cg74-Pgl-Ps123	Cg74-Pgl-Ps124
	Cg74-Pgl-Ps125	Cg74-Pgl-Ps126	Cg74-Pgl-Ps127	Cg74-Pgl-Ps128
	Cg74-Pgl-Ps129	Cg74-Pgl-Ps130	Cg74-Pgl-Ps131	Cg74-Pgl-Ps132
	Cg74-Pgl-Ps133	Cg74-Pgl-Ps134	Cg74-Pgl-Ps135	Cg74-Pgl-Ps136
40	Cg74-Pgl-Ps137	Cg74-Pgl-Ps138	Cg74-Pgl-Ps139	Cg74-Pgl-Ps140
	Cg74-Pgl-Ps141	Cg74-Pgl-Ps142	Cg74-Pgl-Ps143	Cg74-Pgl-Ps144
	Cg74-Pgl-Ps145	Cg74-Pgl-Ps146	Cg74-Pgl-Ps147	Cg74-Pgl-Ps148
	Cg74-Pgl-Ps149	Cg74-Pgl-Ps150	Cg74-Pgl-Ps151	Cg74-Pgl-Ps152
	Cg74-Pgl-Ps153	Cg74-Pgl-Ps154	Cg74-Pgl-Ps155	Cg74-Pgl-Ps156
45	Cg74-Pgl-Ps157	Cg74-Pgl-Ps158	Cg74-Pgl-Ps159	Cg74-Pgl-Ps160
	Cg74-Pgl-Ps161	Cg74-Pgl-Ps162	Cg74-Pgl-Ps163	Cg74-Pgl-Ps164
	Cg74-Pgl-Ps165	Cg74-Pgl-Ps166	Cg74-Pgl-Ps167	Cg74-Pgl-Ps168
	Cg74-Pgl-Ps169	Cg74-Pgl-Ps170	Cg74-Pgl-Ps171	Cg74-Pgl-Ps172
	Cg74-Pgl-Ps173	Cg74-Pgl-Ps174	Cg74-Pgl-Ps175	Cg74-Pgl-Ps176
50	Cg74-Pgl-Ps177	Cg74-Pgl-Ps178	Cg74-Pgl-Ps179	Cg74-Pgl-Ps180
	Cg74-Pgl-Ps181	Cg74-Pgl-Ps182	Cg74-Pgl-Ps183	Cg74-Pgl-Ps184
	Cg74-Pgl-Ps185	Cg74-Pgl-Ps186	Cg74-Pgl-Ps187	Cg74-Pgl-Ps188

-100-

	Cg74-Pg1-Ps189	Cg74-Pg1-Ps190	Cg74-Pg1-Ps191	Cg74-Pg1-Ps192
	Cg74-Pg1-Ps193	Cg74-Pg1-Ps194	Cg74-Pg1-Ps195	Cg74-Pg1-Ps196
	Cg74-Pg1-Ps197	Cg74-Pg1-Ps198	Cg74-Pg1-Ps199	Cg74-Pg1-Ps200
	Cg74-Pg1-Ps201	Cg74-Pg1-Ps202	Cg74-Pg1-Ps203	Cg74-Pg1-Ps204
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	Cg74-Pg1-Ps209	Cg74-Pg1-Ps210	Cg74-Pg1-Ps211	Cg74-Pg1-Ps212
	Cg74-Pg1-Ps213	Cg74-Pg1-Ps214	Cg74-Pg1-Ps215	Cg74-Pg1-Ps216
	Cg74-Pg1-Ps217	Cg74-Pg1-Ps218	Cg74-Pg1-Ps219	Cg74-Pg1-Ps220
	Cg74-Pg1-Ps221	Cg74-Pg1-Ps222	Cg74-Pg1-Ps223	Cg74-Pg1-Ps224
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	Cg74-Pg1-Ps229	Cg74-Pg1-Ps230	Cg74-Pg1-Ps231	Cg74-Pg1-Ps232
	Cg74-Pg1-Ps233	Cg74-Pg1-Ps234	Cg74-Pg1-Ps235	Cg74-Pg1-Ps236
	Cg74-Pg1-Ps237	Cg74-Pg1-Ps238	Cg74-Pg1-Ps239	Cg74-Pg1-Ps240
	Cg74-Pg1-Ps241	Cg74-Pg1-Ps242	Cg74-Pg1-Ps243	
15	Cg75-Pg1-Ps1	Cg75-Pg1-Ps2	Cg75-Pg1-Ps3	Cg75-Pg1-Ps4
	Cg75-Pg1-Ps5	Cg75-Pg1-Ps6	Cg75-Pg1-Ps7	Cg75-Pg1-Ps8
	Cg75-Pg1-Ps9	Cg75-Pg1-Ps10	Cg75-Pg1-Ps11	Cg75-Pg1-Ps12
	Cg75-Pg1-Ps13	Cg75-Pg1-Ps14	Cg75-Pg1-Ps15	Cg75-Pg1-Ps16
20	Cg75-Pg1-Ps17	Cg75-Pg1-Ps18	Cg75-Pg1-Ps19	Cg75-Pg1-Ps20
	Cg75-Pg1-Ps21	Cg75-Pg1-Ps22	Cg75-Pg1-Ps23	Cg75-Pg1-Ps24
	Cg75-Pg1-Ps25	Cg75-Pg1-Ps26	Cg75-Pg1-Ps27	Cg75-Pg1-Ps28
	Cg75-Pg1-Ps29	Cg75-Pg1-Ps30	Cg75-Pg1-Ps31	Cg75-Pg1-Ps32
	Cg75-Pg1-Ps33	Cg75-Pg1-Ps34	Cg75-Pg1-Ps35	Cg75-Pg1-Ps36
25	Cg75-Pg1-Ps37	Cg75-Pg1-Ps38	Cg75-Pg1-Ps39	Cg75-Pg1-Ps40
	Cg75-Pg1-Ps41	Cg75-Pg1-Ps42	Cg75-Pg1-Ps43	Cg75-Pg1-Ps44
	Cg75-Pg1-Ps45	Cg75-Pg1-Ps46	Cg75-Pg1-Ps47	Cg75-Pg1-Ps48
	Cg75-Pg1-Ps49	Cg75-Pg1-Ps50	Cg75-Pg1-Ps51	Cg75-Pg1-Ps52
	Cg75-Pg1-Ps53	Cg75-Pg1-Ps54	Cg75-Pg1-Ps55	Cg75-Pg1-Ps56
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	Cg75-Pg1-Ps61	Cg75-Pg1-Ps62	Cg75-Pg1-Ps63	Cg75-Pg1-Ps64
	Cg75-Pg1-Ps65	Cg75-Pg1-Ps66	Cg75-Pg1-Ps67	Cg75-Pg1-Ps68
	Cg75-Pg1-Ps69	Cg75-Pg1-Ps70	Cg75-Pg1-Ps71	Cg75-Pg1-Ps72
	Cg75-Pg1-Ps73	Cg75-Pg1-Ps74	Cg75-Pg1-Ps75	Cg75-Pg1-Ps76
35	Cg75-Pg1-Ps77	Cg75-Pg1-Ps78	Cg75-Pg1-Ps79	Cg75-Pg1-Ps80
	Cg75-Pg1-Ps81	Cg75-Pg1-Ps82	Cg75-Pg1-Ps83	Cg75-Pg1-Ps84
	Cg75-Pg1-Ps85	Cg75-Pg1-Ps86	Cg75-Pg1-Ps87	Cg75-Pg1-Ps88
	Cg75-Pg1-Ps89	Cg75-Pg1-Ps90	Cg75-Pg1-Ps91	Cg75-Pg1-Ps92
	Cg75-Pg1-Ps93	Cg75-Pg1-Ps94	Cg75-Pg1-Ps95	Cg75-Pg1-Ps96
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	Cg75-Pg1-Ps101	Cg75-Pg1-Ps102	Cg75-Pg1-Ps103	Cg75-Pg1-Ps104
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	Cg75-Pg1-Ps109	Cg75-Pg1-Ps110	Cg75-Pg1-Ps111	Cg75-Pg1-Ps112
	Cg75-Pg1-Ps113	Cg75-Pg1-Ps114	Cg75-Pg1-Ps115	Cg75-Pg1-Ps116
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	Cg75-Pg1-Ps121	Cg75-Pg1-Ps122	Cg75-Pg1-Ps123	Cg75-Pg1-Ps124
	Cg75-Pg1-Ps125	Cg75-Pg1-Ps126	Cg75-Pg1-Ps127	Cg75-Pg1-Ps128
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	Cg75-Pg1-Ps141	Cg75-Pg1-Ps142	Cg75-Pg1-Ps143	Cg75-Pg1-Ps144
	Cg75-Pg1-Ps145	Cg75-Pg1-Ps146	Cg75-Pg1-Ps147	Cg75-Pg1-Ps148

-101-

	Cg75-Pgl-Ps149	Cg75-Pgl-Ps150	Cg75-Pgl-Ps151	Cg75-Pgl-Ps152
	Cg75-Pgl-Ps153	Cg75-Pgl-Ps154	Cg75-Pgl-Ps155	Cg75-Pgl-Ps156
	Cg75-Pgl-Ps157	Cg75-Pgl-Ps158	Cg75-Pgl-Ps159	Cg75-Pgl-Ps160
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	Cg75-Pgl-Ps173	Cg75-Pgl-Ps174	Cg75-Pgl-Ps175	Cg75-Pgl-Ps176
	Cg75-Pgl-Ps177	Cg75-Pgl-Ps178	Cg75-Pgl-Ps179	Cg75-Pgl-Ps180
	Cg75-Pgl-Ps181	Cg75-Pgl-Ps182	Cg75-Pgl-Ps183	Cg75-Pgl-Ps184
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	Cg75-Pgl-Ps193	Cg75-Pgl-Ps194	Cg75-Pgl-Ps195	Cg75-Pgl-Ps196
	Cg75-Pgl-Ps197	Cg75-Pgl-Ps198	Cg75-Pgl-Ps199	Cg75-Pgl-Ps200
	Cg75-Pgl-Ps201	Cg75-Pgl-Ps202	Cg75-Pgl-Ps203	Cg75-Pgl-Ps204
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	Cg75-Pgl-Ps213	Cg75-Pgl-Ps214	Cg75-Pgl-Ps215	Cg75-Pgl-Ps216
	Cg75-Pgl-Ps217	Cg75-Pgl-Ps218	Cg75-Pgl-Ps219	Cg75-Pgl-Ps220
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	Cg75-Pgl-Ps241	Cg75-Pgl-Ps242	Cg75-Pgl-Ps243	
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	Cg76-Pgl-Ps9	Cg76-Pgl-Ps10	Cg76-Pgl-Ps11	Cg76-Pgl-Ps12
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	Cg76-Pgl-Ps25	Cg76-Pgl-Ps26	Cg76-Pgl-Ps27	Cg76-Pgl-Ps28
	Cg76-Pgl-Ps29	Cg76-Pgl-Ps30	Cg76-Pgl-Ps31	Cg76-Pgl-Ps32
	Cg76-Pgl-Ps33	Cg76-Pgl-Ps34	Cg76-Pgl-Ps35	Cg76-Pgl-Ps36
35	Cg76-Pgl-Ps37	Cg76-Pgl-Ps38	Cg76-Pgl-Ps39	Cg76-Pgl-Ps40
	Cg76-Pgl-Ps41	Cg76-Pgl-Ps42	Cg76-Pgl-Ps43	Cg76-Pgl-Ps44
	Cg76-Pgl-Ps45	Cg76-Pgl-Ps46	Cg76-Pgl-Ps47	Cg76-Pgl-Ps48
	Cg76-Pgl-Ps49	Cg76-Pgl-Ps50	Cg76-Pgl-Ps51	Cg76-Pgl-Ps52
	Cg76-Pgl-Ps53	Cg76-Pgl-Ps54	Cg76-Pgl-Ps55	Cg76-Pgl-Ps56
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	Cg76-Pgl-Ps73	Cg76-Pgl-Ps74	Cg76-Pgl-Ps75	Cg76-Pgl-Ps76
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	Cg76-Pgl-Ps101	Cg76-Pgl-Ps102	Cg76-Pgl-Ps103	Cg76-Pgl-Ps104
	Cg76-Pgl-Ps105	Cg76-Pgl-Ps106	Cg76-Pgl-Ps107	Cg76-Pgl-Ps108

-102-

	Cg76-Pgl-Ps109	Cg76-Pgl-Ps110	Cg76-Pgl-Ps111	Cg76-Pgl-Ps112
	Cg76-Pgl-Ps113	Cg76-Pgl-Ps114	Cg76-Pgl-Ps115	Cg76-Pgl-Ps116
	Cg76-Pgl-Ps117	Cg76-Pgl-Ps118	Cg76-Pgl-Ps119	Cg76-Pgl-Ps120
	Cg76-Pgl-Ps121	Cg76-Pgl-Ps122	Cg76-Pgl-Ps123	Cg76-Pgl-Ps124
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	Cg76-Pgl-Ps129	Cg76-Pgl-Ps130	Cg76-Pgl-Ps131	Cg76-Pgl-Ps132
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	Cg76-Pgl-Ps233	Cg76-Pgl-Ps234	Cg76-Pgl-Ps235	Cg76-Pgl-Ps236
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	Cg76-Pgl-Ps241	Cg76-Pgl-Ps242	Cg76-Pgl-Ps243	
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	Cg81-Pgl-Ps45	Cg81-Pgl-Ps46	Cg81-Pgl-Ps47	Cg81-Pgl-Ps48
	Cg81-Pgl-Ps49	Cg81-Pgl-Ps50	Cg81-Pgl-Ps51	Cg81-Pgl-Ps52
	Cg81-Pgl-Ps53	Cg81-Pgl-Ps54	Cg81-Pgl-Ps55	Cg81-Pgl-Ps56
50	Cg81-Pgl-Ps57	Cg81-Pgl-Ps58	Cg81-Pgl-Ps59	Cg81-Pgl-Ps60
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	Cg81-Pgl-Ps65	Cg81-Pgl-Ps66	Cg81-Pgl-Ps67	Cg81-Pgl-Ps68

-103-

	Cg81-Pgl-Ps69	Cg81-Pgl-Ps70	Cg81-Pgl-Ps71	Cg81-Pgl-Ps72
	Cg81-Pgl-Ps73	Cg81-Pgl-Ps74	Cg81-Pgl-Ps75	Cg81-Pgl-Ps76
	Cg81-Pgl-Ps77	Cg81-Pgl-Ps78	Cg81-Pgl-Ps79	Cg81-Pgl-Ps80
	Cg81-Pgl-Ps81	Cg81-Pgl-Ps82	Cg81-Pgl-Ps83	Cg81-Pgl-Ps84
5	Cg81-Pgl-Ps85	Cg81-Pgl-Ps86	Cg81-Pgl-Ps87	Cg81-Pgl-Ps88
	Cg81-Pgl-Ps89	Cg81-Pgl-Ps90	Cg81-Pgl-Ps91	Cg81-Pgl-Ps92
	Cg81-Pgl-Ps93	Cg81-Pgl-Ps94	Cg81-Pgl-Ps95	Cg81-Pgl-Ps96
	Cg81-Pgl-Ps97	Cg81-Pgl-Ps98	Cg81-Pgl-Ps99	Cg81-Pgl-Ps100
	Cg81-Pgl-Ps101	Cg81-Pgl-Ps102	Cg81-Pgl-Ps103	Cg81-Pgl-Ps104
10	Cg81-Pgl-Ps105	Cg81-Pgl-Ps106	Cg81-Pgl-Ps107	Cg81-Pgl-Ps108
	Cg81-Pgl-Ps109	Cg81-Pgl-Ps110	Cg81-Pgl-Ps111	Cg81-Pgl-Ps112
	Cg81-Pgl-Ps113	Cg81-Pgl-Ps114	Cg81-Pgl-Ps115	Cg81-Pgl-Ps116
	Cg81-Pgl-Ps117	Cg81-Pgl-Ps118	Cg81-Pgl-Ps119	Cg81-Pgl-Ps120
	Cg81-Pgl-Ps121	Cg81-Pgl-Ps122	Cg81-Pgl-Ps123	Cg81-Pgl-Ps124
15	Cg81-Pgl-Ps125	Cg81-Pgl-Ps126	Cg81-Pgl-Ps127	Cg81-Pgl-Ps128
	Cg81-Pgl-Ps129	Cg81-Pgl-Ps130	Cg81-Pgl-Ps131	Cg81-Pgl-Ps132
	Cg81-Pgl-Ps133	Cg81-Pgl-Ps134	Cg81-Pgl-Ps135	Cg81-Pgl-Ps136
	Cg81-Pgl-Ps137	Cg81-Pgl-Ps138	Cg81-Pgl-Ps139	Cg81-Pgl-Ps140
	Cg81-Pgl-Ps141	Cg81-Pgl-Ps142	Cg81-Pgl-Ps143	Cg81-Pgl-Ps144
20	Cg81-Pgl-Ps145	Cg81-Pgl-Ps146	Cg81-Pgl-Ps147	Cg81-Pgl-Ps148
	Cg81-Pgl-Ps149	Cg81-Pgl-Ps150	Cg81-Pgl-Ps151	Cg81-Pgl-Ps152
	Cg81-Pgl-Ps153	Cg81-Pgl-Ps154	Cg81-Pgl-Ps155	Cg81-Pgl-Ps156
	Cg81-Pgl-Ps157	Cg81-Pgl-Ps158	Cg81-Pgl-Ps159	Cg81-Pgl-Ps160
	Cg81-Pgl-Ps161	Cg81-Pgl-Ps162	Cg81-Pgl-Ps163	Cg81-Pgl-Ps164
25	Cg81-Pgl-Ps165	Cg81-Pgl-Ps166	Cg81-Pgl-Ps167	Cg81-Pgl-Ps168
	Cg81-Pgl-Ps169	Cg81-Pgl-Ps170	Cg81-Pgl-Ps171	Cg81-Pgl-Ps172
	Cg81-Pgl-Ps173	Cg81-Pgl-Ps174	Cg81-Pgl-Ps175	Cg81-Pgl-Ps176
	Cg81-Pgl-Ps177	Cg81-Pgl-Ps178	Cg81-Pgl-Ps179	Cg81-Pgl-Ps180
	Cg81-Pgl-Ps181	Cg81-Pgl-Ps182	Cg81-Pgl-Ps183	Cg81-Pgl-Ps184
30	Cg81-Pgl-Ps185	Cg81-Pgl-Ps186	Cg81-Pgl-Ps187	Cg81-Pgl-Ps188
	Cg81-Pgl-Ps189	Cg81-Pgl-Ps190	Cg81-Pgl-Ps191	Cg81-Pgl-Ps192
	Cg81-Pgl-Ps193	Cg81-Pgl-Ps194	Cg81-Pgl-Ps195	Cg81-Pgl-Ps196
	Cg81-Pgl-Ps197	Cg81-Pgl-Ps198	Cg81-Pgl-Ps199	Cg81-Pgl-Ps200
	Cg81-Pgl-Ps201	Cg81-Pgl-Ps202	Cg81-Pgl-Ps203	Cg81-Pgl-Ps204
35	Cg81-Pgl-Ps205	Cg81-Pgl-Ps206	Cg81-Pgl-Ps207	Cg81-Pgl-Ps208
	Cg81-Pgl-Ps209	Cg81-Pgl-Ps210	Cg81-Pgl-Ps211	Cg81-Pgl-Ps212
	Cg81-Pgl-Ps213	Cg81-Pgl-Ps214	Cg81-Pgl-Ps215	Cg81-Pgl-Ps216
	Cg81-Pgl-Ps217	Cg81-Pgl-Ps218	Cg81-Pgl-Ps219	Cg81-Pgl-Ps220
	Cg81-Pgl-Ps221	Cg81-Pgl-Ps222	Cg81-Pgl-Ps223	Cg81-Pgl-Ps224
40	Cg81-Pgl-Ps225	Cg81-Pgl-Ps226	Cg81-Pgl-Ps227	Cg81-Pgl-Ps228
	Cg81-Pgl-Ps229	Cg81-Pgl-Ps230	Cg81-Pgl-Ps231	Cg81-Pgl-Ps232
	Cg81-Pgl-Ps233	Cg81-Pgl-Ps234	Cg81-Pgl-Ps235	Cg81-Pgl-Ps236
	Cg81-Pgl-Ps237	Cg81-Pgl-Ps238	Cg81-Pgl-Ps239	Cg81-Pgl-Ps240
	Cg81-Pgl-Ps241	Cg81-Pgl-Ps242	Cg81-Pgl-Ps243	
45	Cg82-Pgl-Ps1	Cg82-Pgl-Ps2	Cg82-Pgl-Ps3	Cg82-Pgl-Ps4
	Cg82-Pgl-Ps5	Cg82-Pgl-Ps6	Cg82-Pgl-Ps7	Cg82-Pgl-Ps8
	Cg82-Pgl-Ps9	Cg82-Pgl-Ps10	Cg82-Pgl-Ps11	Cg82-Pgl-Ps12
	Cg82-Pgl-Ps13	Cg82-Pgl-Ps14	Cg82-Pgl-Ps15	Cg82-Pgl-Ps16
50	Cg82-Pgl-Ps17	Cg82-Pgl-Ps18	Cg82-Pgl-Ps19	Cg82-Pgl-Ps20
	Cg82-Pgl-Ps21	Cg82-Pgl-Ps22	Cg82-Pgl-Ps23	Cg82-Pgl-Ps24
	Cg82-Pgl-Ps25	Cg82-Pgl-Ps26	Cg82-Pgl-Ps27	Cg82-Pgl-Ps28

	Cg82-Pg1-Ps29	Cg82-Pg1-Ps30	Cg82-Pg1-Ps31	Cg82-Pg1-Ps32
	Cg82-Pg1-Ps33	Cg82-Pg1-Ps34	Cg82-Pg1-Ps35	Cg82-Pg1-Ps36
	Cg82-Pg1-Ps37	Cg82-Pg1-Ps38	Cg82-Pg1-Ps39	Cg82-Pg1-Ps40
	Cg82-Pg1-Ps41	Cg82-Pg1-Ps42	Cg82-Pg1-Ps43	Cg82-Pg1-Ps44
5	Cg82-Pg1-Ps45	Cg82-Pg1-Ps46	Cg82-Pg1-Ps47	Cg82-Pg1-Ps48
	Cg82-Pg1-Ps49	Cg82-Pg1-Ps50	Cg82-Pg1-Ps51	Cg82-Pg1-Ps52
	Cg82-Pg1-Ps53	Cg82-Pg1-Ps54	Cg82-Pg1-Ps55	Cg82-Pg1-Ps56
	Cg82-Pg1-Ps57	Cg82-Pg1-Ps58	Cg82-Pg1-Ps59	Cg82-Pg1-Ps60
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	Cg82-Pg1-Ps69	Cg82-Pg1-Ps70	Cg82-Pg1-Ps71	Cg82-Pg1-Ps72
	Cg82-Pg1-Ps73	Cg82-Pg1-Ps74	Cg82-Pg1-Ps75	Cg82-Pg1-Ps76
	Cg82-Pg1-Ps77	Cg82-Pg1-Ps78	Cg82-Pg1-Ps79	Cg82-Pg1-Ps80
	Cg82-Pg1-Ps81	Cg82-Pg1-Ps82	Cg82-Pg1-Ps83	Cg82-Pg1-Ps84
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	Cg82-Pg1-Ps89	Cg82-Pg1-Ps90	Cg82-Pg1-Ps91	Cg82-Pg1-Ps92
	Cg82-Pg1-Ps93	Cg82-Pg1-Ps94	Cg82-Pg1-Ps95	Cg82-Pg1-Ps96
	Cg82-Pg1-Ps97	Cg82-Pg1-Ps98	Cg82-Pg1-Ps99	Cg82-Pg1-Ps100
	Cg82-Pg1-Ps101	Cg82-Pg1-Ps102	Cg82-Pg1-Ps103	Cg82-Pg1-Ps104
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	Cg82-Pg1-Ps109	Cg82-Pg1-Ps110	Cg82-Pg1-Ps111	Cg82-Pg1-Ps112
	Cg82-Pg1-Ps113	Cg82-Pg1-Ps114	Cg82-Pg1-Ps115	Cg82-Pg1-Ps116
	Cg82-Pg1-Ps117	Cg82-Pg1-Ps118	Cg82-Pg1-Ps119	Cg82-Pg1-Ps120
	Cg82-Pg1-Ps121	Cg82-Pg1-Ps122	Cg82-Pg1-Ps123	Cg82-Pg1-Ps124
25	Cg82-Pg1-Ps125	Cg82-Pg1-Ps126	Cg82-Pg1-Ps127	Cg82-Pg1-Ps128
	Cg82-Pg1-Ps129	Cg82-Pg1-Ps130	Cg82-Pg1-Ps131	Cg82-Pg1-Ps132
	Cg82-Pg1-Ps133	Cg82-Pg1-Ps134	Cg82-Pg1-Ps135	Cg82-Pg1-Ps136
	Cg82-Pg1-Ps137	Cg82-Pg1-Ps138	Cg82-Pg1-Ps139	Cg82-Pg1-Ps140
	Cg82-Pg1-Ps141	Cg82-Pg1-Ps142	Cg82-Pg1-Ps143	Cg82-Pg1-Ps144
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	Cg82-Pg1-Ps149	Cg82-Pg1-Ps150	Cg82-Pg1-Ps151	Cg82-Pg1-Ps152
	Cg82-Pg1-Ps153	Cg82-Pg1-Ps154	Cg82-Pg1-Ps155	Cg82-Pg1-Ps156
	Cg82-Pg1-Ps157	Cg82-Pg1-Ps158	Cg82-Pg1-Ps159	Cg82-Pg1-Ps160
	Cg82-Pg1-Ps161	Cg82-Pg1-Ps162	Cg82-Pg1-Ps163	Cg82-Pg1-Ps164
35	Cg82-Pg1-Ps165	Cg82-Pg1-Ps166	Cg82-Pg1-Ps167	Cg82-Pg1-Ps168
	Cg82-Pg1-Ps169	Cg82-Pg1-Ps170	Cg82-Pg1-Ps171	Cg82-Pg1-Ps172
	Cg82-Pg1-Ps173	Cg82-Pg1-Ps174	Cg82-Pg1-Ps175	Cg82-Pg1-Ps176
	Cg82-Pg1-Ps177	Cg82-Pg1-Ps178	Cg82-Pg1-Ps179	Cg82-Pg1-Ps180
	Cg82-Pg1-Ps181	Cg82-Pg1-Ps182	Cg82-Pg1-Ps183	Cg82-Pg1-Ps184
40	Cg82-Pg1-Ps185	Cg82-Pg1-Ps186	Cg82-Pg1-Ps187	Cg82-Pg1-Ps188
	Cg82-Pg1-Ps189	Cg82-Pg1-Ps190	Cg82-Pg1-Ps191	Cg82-Pg1-Ps192
	Cg82-Pg1-Ps193	Cg82-Pg1-Ps194	Cg82-Pg1-Ps195	Cg82-Pg1-Ps196
	Cg82-Pg1-Ps197	Cg82-Pg1-Ps198	Cg82-Pg1-Ps199	Cg82-Pg1-Ps200
	Cg82-Pg1-Ps201	Cg82-Pg1-Ps202	Cg82-Pg1-Ps203	Cg82-Pg1-Ps204
45	Cg82-Pg1-Ps205	Cg82-Pg1-Ps206	Cg82-Pg1-Ps207	Cg82-Pg1-Ps208
	Cg82-Pg1-Ps209	Cg82-Pg1-Ps210	Cg82-Pg1-Ps211	Cg82-Pg1-Ps212
	Cg82-Pg1-Ps213	Cg82-Pg1-Ps214	Cg82-Pg1-Ps215	Cg82-Pg1-Ps216
	Cg82-Pg1-Ps217	Cg82-Pg1-Ps218	Cg82-Pg1-Ps219	Cg82-Pg1-Ps220
	Cg82-Pg1-Ps221	Cg82-Pg1-Ps222	Cg82-Pg1-Ps223	Cg82-Pg1-Ps224
50	Cg82-Pg1-Ps225	Cg82-Pg1-Ps226	Cg82-Pg1-Ps227	Cg82-Pg1-Ps228
	Cg82-Pg1-Ps229	Cg82-Pg1-Ps230	Cg82-Pg1-Ps231	Cg82-Pg1-Ps232
	Cg82-Pg1-Ps233	Cg82-Pg1-Ps234	Cg82-Pg1-Ps235	Cg82-Pg1-Ps236

-105-

	Cg82-Pg1-Ps237 Cg82-Pg1-Ps241	Cg82-Pg1-Ps238 Cg82-Pg1-Ps242	Cg82-Pg1-Ps239 Cg82-Pg1-Ps243	Cg82-Pg1-Ps240
5	Cg83-Pg1-Ps1 Cg83-Pg1-Ps5 Cg83-Pg1-Ps9 Cg83-Pg1-Ps13 Cg83-Pg1-Ps17	Cg83-Pg1-Ps2 Cg83-Pg1-Ps6 Cg83-Pg1-Ps10 Cg83-Pg1-Ps14 Cg83-Pg1-Ps18	Cg83-Pg1-Ps3 Cg83-Pg1-Ps7 Cg83-Pg1-Ps11 Cg83-Pg1-Ps15 Cg83-Pg1-Ps19	Cg83-Pg1-Ps4 Cg83-Pg1-Ps8 Cg83-Pg1-Ps12 Cg83-Pg1-Ps16 Cg83-Pg1-Ps20
10	Cg83-Pg1-Ps21 Cg83-Pg1-Ps25 Cg83-Pg1-Ps29 Cg83-Pg1-Ps33 Cg83-Pg1-Ps37	Cg83-Pg1-Ps22 Cg83-Pg1-Ps26 Cg83-Pg1-Ps30 Cg83-Pg1-Ps34 Cg83-Pg1-Ps38	Cg83-Pg1-Ps23 Cg83-Pg1-Ps27 Cg83-Pg1-Ps31 Cg83-Pg1-Ps35 Cg83-Pg1-Ps39	Cg83-Pg1-Ps24 Cg83-Pg1-Ps28 Cg83-Pg1-Ps32 Cg83-Pg1-Ps36 Cg83-Pg1-Ps40
15	Cg83-Pg1-Ps41 Cg83-Pg1-Ps45 Cg83-Pg1-Ps49 Cg83-Pg1-Ps53 Cg83-Pg1-Ps57	Cg83-Pg1-Ps42 Cg83-Pg1-Ps46 Cg83-Pg1-Ps50 Cg83-Pg1-Ps54 Cg83-Pg1-Ps58	Cg83-Pg1-Ps43 Cg83-Pg1-Ps47 Cg83-Pg1-Ps51 Cg83-Pg1-Ps55 Cg83-Pg1-Ps59	Cg83-Pg1-Ps44 Cg83-Pg1-Ps48 Cg83-Pg1-Ps52 Cg83-Pg1-Ps56 Cg83-Pg1-Ps60
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-106-

	Cg83-Pg1-Ps193	Cg83-Pg1-Ps194	Cg83-Pg1-Ps195	Cg83-Pg1-Ps196
	Cg83-Pg1-Ps197	Cg83-Pg1-Ps198	Cg83-Pg1-Ps199	Cg83-Pg1-Ps200
	Cg83-Pg1-Ps201	Cg83-Pg1-Ps202	Cg83-Pg1-Ps203	Cg83-Pg1-Ps204
	Cg83-Pg1-Ps205	Cg83-Pg1-Ps206	Cg83-Pg1-Ps207	Cg83-Pg1-Ps208
5	Cg83-Pg1-Ps209	Cg83-Pg1-Ps210	Cg83-Pg1-Ps211	Cg83-Pg1-Ps212
	Cg83-Pg1-Ps213	Cg83-Pg1-Ps214	Cg83-Pg1-Ps215	Cg83-Pg1-Ps216
	Cg83-Pg1-Ps217	Cg83-Pg1-Ps218	Cg83-Pg1-Ps219	Cg83-Pg1-Ps220
	Cg83-Pg1-Ps221	Cg83-Pg1-Ps222	Cg83-Pg1-Ps223	Cg83-Pg1-Ps224
	Cg83-Pg1-Ps225	Cg83-Pg1-Ps226	Cg83-Pg1-Ps227	Cg83-Pg1-Ps228
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	Cg83-Pg1-Ps233	Cg83-Pg1-Ps234	Cg83-Pg1-Ps235	Cg83-Pg1-Ps236
	Cg83-Pg1-Ps237	Cg83-Pg1-Ps238	Cg83-Pg1-Ps239	Cg83-Pg1-Ps240
	Cg83-Pg1-Ps241	Cg83-Pg1-Ps242	Cg83-Pg1-Ps243	
15	Cg84-Pg1-Ps1	Cg84-Pg1-Ps2	Cg84-Pg1-Ps3	Cg84-Pg1-Ps4
	Cg84-Pg1-Ps5	Cg84-Pg1-Ps6	Cg84-Pg1-Ps7	Cg84-Pg1-Ps8
	Cg84-Pg1-Ps9	Cg84-Pg1-Ps10	Cg84-Pg1-Ps11	Cg84-Pg1-Ps12
	Cg84-Pg1-Ps13	Cg84-Pg1-Ps14	Cg84-Pg1-Ps15	Cg84-Pg1-Ps16
	Cg84-Pg1-Ps17	Cg84-Pg1-Ps18	Cg84-Pg1-Ps19	Cg84-Pg1-Ps20
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	Cg84-Pg1-Ps25	Cg84-Pg1-Ps26	Cg84-Pg1-Ps27	Cg84-Pg1-Ps28
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	Cg84-Pg1-Ps33	Cg84-Pg1-Ps34	Cg84-Pg1-Ps35	Cg84-Pg1-Ps36
	Cg84-Pg1-Ps37	Cg84-Pg1-Ps38	Cg84-Pg1-Ps39	Cg84-Pg1-Ps40
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	Cg84-Pg1-Ps45	Cg84-Pg1-Ps46	Cg84-Pg1-Ps47	Cg84-Pg1-Ps48
	Cg84-Pg1-Ps49	Cg84-Pg1-Ps50	Cg84-Pg1-Ps51	Cg84-Pg1-Ps52
	Cg84-Pg1-Ps53	Cg84-Pg1-Ps54	Cg84-Pg1-Ps55	Cg84-Pg1-Ps56
	Cg84-Pg1-Ps57	Cg84-Pg1-Ps58	Cg84-Pg1-Ps59	Cg84-Pg1-Ps60
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	Cg84-Pg1-Ps65	Cg84-Pg1-Ps66	Cg84-Pg1-Ps67	Cg84-Pg1-Ps68
	Cg84-Pg1-Ps69	Cg84-Pg1-Ps70	Cg84-Pg1-Ps71	Cg84-Pg1-Ps72
	Cg84-Pg1-Ps73	Cg84-Pg1-Ps74	Cg84-Pg1-Ps75	Cg84-Pg1-Ps76
	Cg84-Pg1-Ps77	Cg84-Pg1-Ps78	Cg84-Pg1-Ps79	Cg84-Pg1-Ps80
35	Cg84-Pg1-Ps81	Cg84-Pg1-Ps82	Cg84-Pg1-Ps83	Cg84-Pg1-Ps84
	Cg84-Pg1-Ps85	Cg84-Pg1-Ps86	Cg84-Pg1-Ps87	Cg84-Pg1-Ps88
	Cg84-Pg1-Ps89	Cg84-Pg1-Ps90	Cg84-Pg1-Ps91	Cg84-Pg1-Ps92
	Cg84-Pg1-Ps93	Cg84-Pg1-Ps94	Cg84-Pg1-Ps95	Cg84-Pg1-Ps96
	Cg84-Pg1-Ps97	Cg84-Pg1-Ps98	Cg84-Pg1-Ps99	Cg84-Pg1-Ps100
40	Cg84-Pg1-Ps101	Cg84-Pg1-Ps102	Cg84-Pg1-Ps103	Cg84-Pg1-Ps104
	Cg84-Pg1-Ps105	Cg84-Pg1-Ps106	Cg84-Pg1-Ps107	Cg84-Pg1-Ps108
	Cg84-Pg1-Ps109	Cg84-Pg1-Ps110	Cg84-Pg1-Ps111	Cg84-Pg1-Ps112
	Cg84-Pg1-Ps113	Cg84-Pg1-Ps114	Cg84-Pg1-Ps115	Cg84-Pg1-Ps116
	Cg84-Pg1-Ps117	Cg84-Pg1-Ps118	Cg84-Pg1-Ps119	Cg84-Pg1-Ps120
45	Cg84-Pg1-Ps121	Cg84-Pg1-Ps122	Cg84-Pg1-Ps123	Cg84-Pg1-Ps124
	Cg84-Pg1-Ps125	Cg84-Pg1-Ps126	Cg84-Pg1-Ps127	Cg84-Pg1-Ps128
	Cg84-Pg1-Ps129	Cg84-Pg1-Ps130	Cg84-Pg1-Ps131	Cg84-Pg1-Ps132
	Cg84-Pg1-Ps133	Cg84-Pg1-Ps134	Cg84-Pg1-Ps135	Cg84-Pg1-Ps136
	Cg84-Pg1-Ps137	Cg84-Pg1-Ps138	Cg84-Pg1-Ps139	Cg84-Pg1-Ps140
50	Cg84-Pg1-Ps141	Cg84-Pg1-Ps142	Cg84-Pg1-Ps143	Cg84-Pg1-Ps144
	Cg84-Pg1-Ps145	Cg84-Pg1-Ps146	Cg84-Pg1-Ps147	Cg84-Pg1-Ps148
	Cg84-Pg1-Ps149	Cg84-Pg1-Ps150	Cg84-Pg1-Ps151	Cg84-Pg1-Ps152

-107-

	Cg84-Pg1-Ps153	Cg84-Pg1-Ps154	Cg84-Pg1-Ps155	Cg84-Pg1-Ps156
	Cg84-Pg1-Ps157	Cg84-Pg1-Ps158	Cg84-Pg1-Ps159	Cg84-Pg1-Ps160
	Cg84-Pg1-Ps161	Cg84-Pg1-Ps162	Cg84-Pg1-Ps163	Cg84-Pg1-Ps164
	Cg84-Pg1-Ps165	Cg84-Pg1-Ps166	Cg84-Pg1-Ps167	Cg84-Pg1-Ps168
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	Cg84-Pg1-Ps173	Cg84-Pg1-Ps174	Cg84-Pg1-Ps175	Cg84-Pg1-Ps176
	Cg84-Pg1-Ps177	Cg84-Pg1-Ps178	Cg84-Pg1-Ps179	Cg84-Pg1-Ps180
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	Cg84-Pg1-Ps185	Cg84-Pg1-Ps186	Cg84-Pg1-Ps187	Cg84-Pg1-Ps188
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	Cg84-Pg1-Ps193	Cg84-Pg1-Ps194	Cg84-Pg1-Ps195	Cg84-Pg1-Ps196
	Cg84-Pg1-Ps197	Cg84-Pg1-Ps198	Cg84-Pg1-Ps199	Cg84-Pg1-Ps200
	Cg84-Pg1-Ps201	Cg84-Pg1-Ps202	Cg84-Pg1-Ps203	Cg84-Pg1-Ps204
	Cg84-Pg1-Ps205	Cg84-Pg1-Ps206	Cg84-Pg1-Ps207	Cg84-Pg1-Ps208
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	Cg84-Pg1-Ps217	Cg84-Pg1-Ps218	Cg84-Pg1-Ps219	Cg84-Pg1-Ps220
	Cg84-Pg1-Ps221	Cg84-Pg1-Ps222	Cg84-Pg1-Ps223	Cg84-Pg1-Ps224
	Cg84-Pg1-Ps225	Cg84-Pg1-Ps226	Cg84-Pg1-Ps227	Cg84-Pg1-Ps228
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	Cg84-Pg1-Ps233	Cg84-Pg1-Ps234	Cg84-Pg1-Ps235	Cg84-Pg1-Ps236
	Cg84-Pg1-Ps237	Cg84-Pg1-Ps238	Cg84-Pg1-Ps239	Cg84-Pg1-Ps240
	Cg84-Pg1-Ps241	Cg84-Pg1-Ps242	Cg84-Pg1-Ps243	
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	Cg85-Pg1-Ps5	Cg85-Pg1-Ps6	Cg85-Pg1-Ps7	Cg85-Pg1-Ps8
	Cg85-Pg1-Ps9	Cg85-Pg1-Ps10	Cg85-Pg1-Ps11	Cg85-Pg1-Ps12
	Cg85-Pg1-Ps13	Cg85-Pg1-Ps14	Cg85-Pg1-Ps15	Cg85-Pg1-Ps16
	Cg85-Pg1-Ps17	Cg85-Pg1-Ps18	Cg85-Pg1-Ps19	Cg85-Pg1-Ps20
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	Cg85-Pg1-Ps25	Cg85-Pg1-Ps26	Cg85-Pg1-Ps27	Cg85-Pg1-Ps28
	Cg85-Pg1-Ps29	Cg85-Pg1-Ps30	Cg85-Pg1-Ps31	Cg85-Pg1-Ps32
	Cg85-Pg1-Ps33	Cg85-Pg1-Ps34	Cg85-Pg1-Ps35	Cg85-Pg1-Ps36
	Cg85-Pg1-Ps37	Cg85-Pg1-Ps38	Cg85-Pg1-Ps39	Cg85-Pg1-Ps40
35	Cg85-Pg1-Ps41	Cg85-Pg1-Ps42	Cg85-Pg1-Ps43	Cg85-Pg1-Ps44
	Cg85-Pg1-Ps45	Cg85-Pg1-Ps46	Cg85-Pg1-Ps47	Cg85-Pg1-Ps48
	Cg85-Pg1-Ps49	Cg85-Pg1-Ps50	Cg85-Pg1-Ps51	Cg85-Pg1-Ps52
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	Cg85-Pg1-Ps57	Cg85-Pg1-Ps58	Cg85-Pg1-Ps59	Cg85-Pg1-Ps60
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	Cg85-Pg1-Ps69	Cg85-Pg1-Ps70	Cg85-Pg1-Ps71	Cg85-Pg1-Ps72
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	Cg85-Pg1-Ps77	Cg85-Pg1-Ps78	Cg85-Pg1-Ps79	Cg85-Pg1-Ps80
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	Cg85-Pg1-Ps85	Cg85-Pg1-Ps86	Cg85-Pg1-Ps87	Cg85-Pg1-Ps88
	Cg85-Pg1-Ps89	Cg85-Pg1-Ps90	Cg85-Pg1-Ps91	Cg85-Pg1-Ps92
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	Cg85-Pg1-Ps105	Cg85-Pg1-Ps106	Cg85-Pg1-Ps107	Cg85-Pg1-Ps108
	Cg85-Pg1-Ps109	Cg85-Pg1-Ps110	Cg85-Pg1-Ps111	Cg85-Pg1-Ps112

-108-

5	Cg85-Pgl-Ps113	Cg85-Pgl-Ps114	Cg85-Pgl-Ps115	Cg85-Pgl-Ps116
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	Cg85-Pgl-Ps121	Cg85-Pgl-Ps122	Cg85-Pgl-Ps123	Cg85-Pgl-Ps124
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	Cg86-Pgl-Ps57	Cg86-Pgl-Ps58	Cg86-Pgl-Ps59	Cg86-Pgl-Ps60
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	Cg86-Pgl-Ps69	Cg86-Pgl-Ps70	Cg86-Pgl-Ps71	Cg86-Pgl-Ps72

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	Cg86-Pg1-Ps81	Cg86-Pg1-Ps82	Cg86-Pg1-Ps83	Cg86-Pg1-Ps84
	Cg86-Pg1-Ps85	Cg86-Pg1-Ps86	Cg86-Pg1-Ps87	Cg86-Pg1-Ps88
5	Cg86-Pg1-Ps89	Cg86-Pg1-Ps90	Cg86-Pg1-Ps91	Cg86-Pg1-Ps92
	Cg86-Pg1-Ps93	Cg86-Pg1-Ps94	Cg86-Pg1-Ps95	Cg86-Pg1-Ps96
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	Cg86-Pg1-Ps201	Cg86-Pg1-Ps202	Cg86-Pg1-Ps203	Cg86-Pg1-Ps204
	Cg86-Pg1-Ps205	Cg86-Pg1-Ps206	Cg86-Pg1-Ps207	Cg86-Pg1-Ps208
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	Cg87-Pg1-Ps29	Cg87-Pg1-Ps30	Cg87-Pg1-Ps31	Cg87-Pg1-Ps32

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	Cg87-Pgl-Ps85	Cg87-Pgl-Ps86	Cg87-Pgl-Ps87	Cg87-Pgl-Ps88
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	Cg87-Pgl-Ps93	Cg87-Pgl-Ps94	Cg87-Pgl-Ps95	Cg87-Pgl-Ps96
	Cg87-Pgl-Ps97	Cg87-Pgl-Ps98	Cg87-Pgl-Ps99	Cg87-Pgl-Ps100
	Cg87-Pgl-Ps101	Cg87-Pgl-Ps102	Cg87-Pgl-Ps103	Cg87-Pgl-Ps104
	Cg87-Pgl-Ps105	Cg87-Pgl-Ps106	Cg87-Pgl-Ps107	Cg87-Pgl-Ps108
20	Cg87-Pgl-Ps109	Cg87-Pgl-Ps110	Cg87-Pgl-Ps111	Cg87-Pgl-Ps112
	Cg87-Pgl-Ps113	Cg87-Pgl-Ps114	Cg87-Pgl-Ps115	Cg87-Pgl-Ps116
	Cg87-Pgl-Ps117	Cg87-Pgl-Ps118	Cg87-Pgl-Ps119	Cg87-Pgl-Ps120
	Cg87-Pgl-Ps121	Cg87-Pgl-Ps122	Cg87-Pgl-Ps123	Cg87-Pgl-Ps124
	Cg87-Pgl-Ps125	Cg87-Pgl-Ps126	Cg87-Pgl-Ps127	Cg87-Pgl-Ps128
25	Cg87-Pgl-Ps129	Cg87-Pgl-Ps130	Cg87-Pgl-Ps131	Cg87-Pgl-Ps132
	Cg87-Pgl-Ps133	Cg87-Pgl-Ps134	Cg87-Pgl-Ps135	Cg87-Pgl-Ps136
	Cg87-Pgl-Ps137	Cg87-Pgl-Ps138	Cg87-Pgl-Ps139	Cg87-Pgl-Ps140
	Cg87-Pgl-Ps141	Cg87-Pgl-Ps142	Cg87-Pgl-Ps143	Cg87-Pgl-Ps144
	Cg87-Pgl-Ps145	Cg87-Pgl-Ps146	Cg87-Pgl-Ps147	Cg87-Pgl-Ps148
30	Cg87-Pgl-Ps149	Cg87-Pgl-Ps150	Cg87-Pgl-Ps151	Cg87-Pgl-Ps152
	Cg87-Pgl-Ps153	Cg87-Pgl-Ps154	Cg87-Pgl-Ps155	Cg87-Pgl-Ps156
	Cg87-Pgl-Ps157	Cg87-Pgl-Ps158	Cg87-Pgl-Ps159	Cg87-Pgl-Ps160
	Cg87-Pgl-Ps161	Cg87-Pgl-Ps162	Cg87-Pgl-Ps163	Cg87-Pgl-Ps164
	Cg87-Pgl-Ps165	Cg87-Pgl-Ps166	Cg87-Pgl-Ps167	Cg87-Pgl-Ps168
35	Cg87-Pgl-Ps169	Cg87-Pgl-Ps170	Cg87-Pgl-Ps171	Cg87-Pgl-Ps172
	Cg87-Pgl-Ps173	Cg87-Pgl-Ps174	Cg87-Pgl-Ps175	Cg87-Pgl-Ps176
	Cg87-Pgl-Ps177	Cg87-Pgl-Ps178	Cg87-Pgl-Ps179	Cg87-Pgl-Ps180
	Cg87-Pgl-Ps181	Cg87-Pgl-Ps182	Cg87-Pgl-Ps183	Cg87-Pgl-Ps184
	Cg87-Pgl-Ps185	Cg87-Pgl-Ps186	Cg87-Pgl-Ps187	Cg87-Pgl-Ps188
40	Cg87-Pgl-Ps189	Cg87-Pgl-Ps190	Cg87-Pgl-Ps191	Cg87-Pgl-Ps192
	Cg87-Pgl-Ps193	Cg87-Pgl-Ps194	Cg87-Pgl-Ps195	Cg87-Pgl-Ps196
	Cg87-Pgl-Ps197	Cg87-Pgl-Ps198	Cg87-Pgl-Ps199	Cg87-Pgl-Ps200
	Cg87-Pgl-Ps201	Cg87-Pgl-Ps202	Cg87-Pgl-Ps203	Cg87-Pgl-Ps204
	Cg87-Pgl-Ps205	Cg87-Pgl-Ps206	Cg87-Pgl-Ps207	Cg87-Pgl-Ps208
45	Cg87-Pgl-Ps209	Cg87-Pgl-Ps210	Cg87-Pgl-Ps211	Cg87-Pgl-Ps212
	Cg87-Pgl-Ps213	Cg87-Pgl-Ps214	Cg87-Pgl-Ps215	Cg87-Pgl-Ps216
	Cg87-Pgl-Ps217	Cg87-Pgl-Ps218	Cg87-Pgl-Ps219	Cg87-Pgl-Ps220
	Cg87-Pgl-Ps221	Cg87-Pgl-Ps222	Cg87-Pgl-Ps223	Cg87-Pgl-Ps224
	Cg87-Pgl-Ps225	Cg87-Pgl-Ps226	Cg87-Pgl-Ps227	Cg87-Pgl-Ps228
50	Cg87-Pgl-Ps229	Cg87-Pgl-Ps230	Cg87-Pgl-Ps231	Cg87-Pgl-Ps232
	Cg87-Pgl-Ps233	Cg87-Pgl-Ps234	Cg87-Pgl-Ps235	Cg87-Pgl-Ps236
	Cg87-Pgl-Ps237	Cg87-Pgl-Ps238	Cg87-Pgl-Ps239	Cg87-Pgl-Ps240

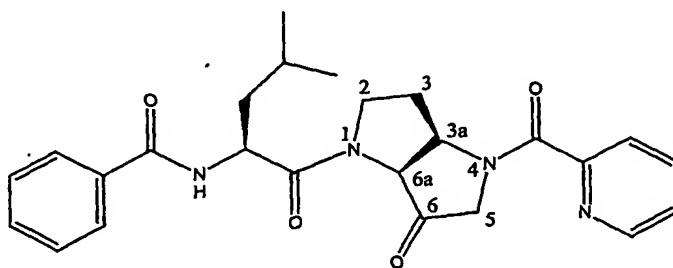
-111-

	Cg87-Pg1-Ps241	Cg87-Pg1-Ps242	Cg87-Pg1-Ps243	
	Cg88-Pg1-Ps1	Cg88-Pg1-Ps2	Cg88-Pg1-Ps3	Cg88-Pg1-Ps4
	Cg88-Pg1-Ps5	Cg88-Pg1-Ps6	Cg88-Pg1-Ps7	Cg88-Pg1-Ps8
5	Cg88-Pg1-Ps9	Cg88-Pg1-Ps10	Cg88-Pg1-Ps11	Cg88-Pg1-Ps12
	Cg88-Pg1-Ps13	Cg88-Pg1-Ps14	Cg88-Pg1-Ps15	Cg88-Pg1-Ps16
	Cg88-Pg1-Ps17	Cg88-Pg1-Ps18	Cg88-Pg1-Ps19	Cg88-Pg1-Ps20
	Cg88-Pg1-Ps21	Cg88-Pg1-Ps22	Cg88-Pg1-Ps23	Cg88-Pg1-Ps24
	Cg88-Pg1-Ps25	Cg88-Pg1-Ps26	Cg88-Pg1-Ps27	Cg88-Pg1-Ps28
10	Cg88-Pg1-Ps29	Cg88-Pg1-Ps30	Cg88-Pg1-Ps31	Cg88-Pg1-Ps32
	Cg88-Pg1-Ps33	Cg88-Pg1-Ps34	Cg88-Pg1-Ps35	Cg88-Pg1-Ps36
	Cg88-Pg1-Ps37	Cg88-Pg1-Ps38	Cg88-Pg1-Ps39	Cg88-Pg1-Ps40
	Cg88-Pg1-Ps41	Cg88-Pg1-Ps42	Cg88-Pg1-Ps43	Cg88-Pg1-Ps44
	Cg88-Pg1-Ps45	Cg88-Pg1-Ps46	Cg88-Pg1-Ps47	Cg88-Pg1-Ps48
15	Cg88-Pg1-Ps49	Cg88-Pg1-Ps50	Cg88-Pg1-Ps51	Cg88-Pg1-Ps52
	Cg88-Pg1-Ps53	Cg88-Pg1-Ps54	Cg88-Pg1-Ps55	Cg88-Pg1-Ps56
	Cg88-Pg1-Ps57	Cg88-Pg1-Ps58	Cg88-Pg1-Ps59	Cg88-Pg1-Ps60
	Cg88-Pg1-Ps61	Cg88-Pg1-Ps62	Cg88-Pg1-Ps63	Cg88-Pg1-Ps64
	Cg88-Pg1-Ps65	Cg88-Pg1-Ps66	Cg88-Pg1-Ps67	Cg88-Pg1-Ps68
20	Cg88-Pg1-Ps69	Cg88-Pg1-Ps70	Cg88-Pg1-Ps71	Cg88-Pg1-Ps72
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	Cg88-Pg1-Ps77	Cg88-Pg1-Ps78	Cg88-Pg1-Ps79	Cg88-Pg1-Ps80
	Cg88-Pg1-Ps81	Cg88-Pg1-Ps82	Cg88-Pg1-Ps83	Cg88-Pg1-Ps84
	Cg88-Pg1-Ps85	Cg88-Pg1-Ps86	Cg88-Pg1-Ps87	Cg88-Pg1-Ps88
25	Cg88-Pg1-Ps89	Cg88-Pg1-Ps90	Cg88-Pg1-Ps91	Cg88-Pg1-Ps92
	Cg88-Pg1-Ps93	Cg88-Pg1-Ps94	Cg88-Pg1-Ps95	Cg88-Pg1-Ps96
	Cg88-Pg1-Ps97	Cg88-Pg1-Ps98	Cg88-Pg1-Ps99	Cg88-Pg1-Ps100
	Cg88-Pg1-Ps101	Cg88-Pg1-Ps102	Cg88-Pg1-Ps103	Cg88-Pg1-Ps104
	Cg88-Pg1-Ps105	Cg88-Pg1-Ps106	Cg88-Pg1-Ps107	Cg88-Pg1-Ps108
30	Cg88-Pg1-Ps109	Cg88-Pg1-Ps110	Cg88-Pg1-Ps111	Cg88-Pg1-Ps112
	Cg88-Pg1-Ps113	Cg88-Pg1-Ps114	Cg88-Pg1-Ps115	Cg88-Pg1-Ps116
	Cg88-Pg1-Ps117	Cg88-Pg1-Ps118	Cg88-Pg1-Ps119	Cg88-Pg1-Ps120
	Cg88-Pg1-Ps121	Cg88-Pg1-Ps122	Cg88-Pg1-Ps123	Cg88-Pg1-Ps124
	Cg88-Pg1-Ps125	Cg88-Pg1-Ps126	Cg88-Pg1-Ps127	Cg88-Pg1-Ps128
35	Cg88-Pg1-Ps129	Cg88-Pg1-Ps130	Cg88-Pg1-Ps131	Cg88-Pg1-Ps132
	Cg88-Pg1-Ps133	Cg88-Pg1-Ps134	Cg88-Pg1-Ps135	Cg88-Pg1-Ps136
	Cg88-Pg1-Ps137	Cg88-Pg1-Ps138	Cg88-Pg1-Ps139	Cg88-Pg1-Ps140
	Cg88-Pg1-Ps141	Cg88-Pg1-Ps142	Cg88-Pg1-Ps143	Cg88-Pg1-Ps144
	Cg88-Pg1-Ps145	Cg88-Pg1-Ps146	Cg88-Pg1-Ps147	Cg88-Pg1-Ps148
40	Cg88-Pg1-Ps149	Cg88-Pg1-Ps150	Cg88-Pg1-Ps151	Cg88-Pg1-Ps152
	Cg88-Pg1-Ps153	Cg88-Pg1-Ps154	Cg88-Pg1-Ps155	Cg88-Pg1-Ps156
	Cg88-Pg1-Ps157	Cg88-Pg1-Ps158	Cg88-Pg1-Ps159	Cg88-Pg1-Ps160
	Cg88-Pg1-Ps161	Cg88-Pg1-Ps162	Cg88-Pg1-Ps163	Cg88-Pg1-Ps164
	Cg88-Pg1-Ps165	Cg88-Pg1-Ps166	Cg88-Pg1-Ps167	Cg88-Pg1-Ps168
45	Cg88-Pg1-Ps169	Cg88-Pg1-Ps170	Cg88-Pg1-Ps171	Cg88-Pg1-Ps172
	Cg88-Pg1-Ps173	Cg88-Pg1-Ps174	Cg88-Pg1-Ps175	Cg88-Pg1-Ps176
	Cg88-Pg1-Ps177	Cg88-Pg1-Ps178	Cg88-Pg1-Ps179	Cg88-Pg1-Ps180
	Cg88-Pg1-Ps181	Cg88-Pg1-Ps182	Cg88-Pg1-Ps183	Cg88-Pg1-Ps184
	Cg88-Pg1-Ps185	Cg88-Pg1-Ps186	Cg88-Pg1-Ps187	Cg88-Pg1-Ps188
50	Cg88-Pg1-Ps189	Cg88-Pg1-Ps190	Cg88-Pg1-Ps191	Cg88-Pg1-Ps192
	Cg88-Pg1-Ps193	Cg88-Pg1-Ps194	Cg88-Pg1-Ps195	Cg88-Pg1-Ps196
	Cg88-Pg1-Ps197	Cg88-Pg1-Ps198	Cg88-Pg1-Ps199	Cg88-Pg1-Ps200

-112-

	Cg88-Pgl-Ps201	Cg88-Pgl-Ps202	Cg88-Pgl-Ps203	Cg88-Pgl-Ps204
	Cg88-Pgl-Ps205	Cg88-Pgl-Ps206	Cg88-Pgl-Ps207	Cg88-Pgl-Ps208
	Cg88-Pgl-Ps209	Cg88-Pgl-Ps210	Cg88-Pgl-Ps211	Cg88-Pgl-Ps212
	Cg88-Pgl-Ps213	Cg88-Pgl-Ps214	Cg88-Pgl-Ps215	Cg88-Pgl-Ps216
5	Cg88-Pgl-Ps217	Cg88-Pgl-Ps218	Cg88-Pgl-Ps219	Cg88-Pgl-Ps220
	Cg88-Pgl-Ps221	Cg88-Pgl-Ps222	Cg88-Pgl-Ps223	Cg88-Pgl-Ps224
	Cg88-Pgl-Ps225	Cg88-Pgl-Ps226	Cg88-Pgl-Ps227	Cg88-Pgl-Ps228
	Cg88-Pgl-Ps229	Cg88-Pgl-Ps230	Cg88-Pgl-Ps231	Cg88-Pgl-Ps232
	Cg88-Pgl-Ps233	Cg88-Pgl-Ps234	Cg88-Pgl-Ps235	Cg88-Pgl-Ps236
10	Cg88-Pgl-Ps237	Cg88-Pgl-Ps238	Cg88-Pgl-Ps239	Cg88-Pgl-Ps240
	Cg88-Pgl-Ps241	Cg88-Pgl-Ps242	Cg88-Pgl-Ps243	

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe compounds of the present invention, following the general guidelines presented by the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9-, 1984. Compounds of formula (I) and the intermediates and starting materials used in their preparation are named in accordance with the IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group. An example compound of formula (I), compound (1) in which Z is CH₂, R¹ is R²C(O), where R² is 2-pyridyl, P₁, P₂ are methylene, Y is 4-methylpentoyl, (X)₀ is zero, (W)_n is NH, (V)_m is C(O) and U is phenyl is thus named:-



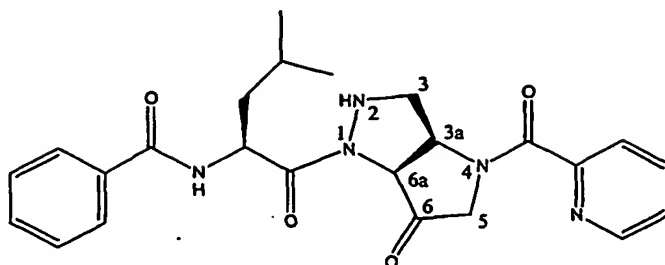
(1)

(3aR,6aS)-N-{(1S)-3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydropyrrolo [3,2-b]pyrrole-1-carbonyl]-butyl}-benzamide;

A second example compound of formula (I), compound (2) in which Z is CH₂, R¹ is R²C(O), where R² is 2-pyridyl, P₁, is methylene, P₂ is NH, Y is 4-

-113-

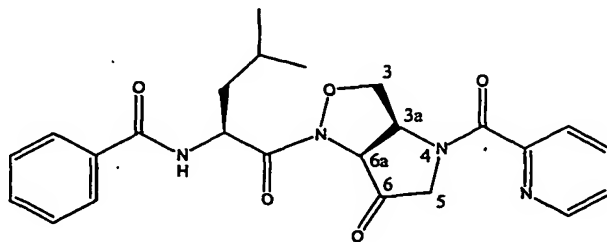
methylpentoyl, $(X)_0$ is zero, $(W)_n$ is NH, $(V)_m$ is C(O) and U is phenyl is thus named:-



(2)

- 5 (3aR,6aS)-N-{(1S)-3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydropyrrolo
[3,2-c]pyrazole-1-carbonyl]-butyl}-benzamide;

A third example compound of formula (I), compound (3) in which Z is CH₂, R¹ is R²C(O), where R² is 2-pyridyl, P₁ is methylene, P₂ is O, Y is 4-methylpentoyl,
10 (X)₀ is zero, (W)_n is NH, (V)_m is C(O) and U is phenyl is thus named:-



(3)

15

- (3aS, 6aS)-N-{(1S)-3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-2-oxa-
1,4-diaza-pentalene-1-carbonyl]-butyl}-benzamide.

Compounds of the invention include, but are not limited to, the following
20 examples where all 4 stereoisomeric combinations of the bicyclic ketone are
included where P₂ is CH₂, i.e. (3aS, 6aS), (3aR, 6aS), (3aS, 6aR), (3aR, 6aR) and
also included are the equivalent analogues where P₂ is O and NH. More preferred

compounds consist of the cis-bicyclic isomers which, when P₂ is CH₂, are designated as (3aR, 6aS) and (3aS, 6aR) and also more preferred are the equivalent cis-bicyclic analogues where P₂ is O and NH.

- 5 4. Naphthalene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
5. Quinoline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 6. Benzo[*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
7. Benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 8. Biphenyl-4-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
9. 4-*tert*-Butyl-N-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 10. 4-Dimethylamino-N-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 11. 7-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
12. {3-Methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
- 30 13. 5-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
14. Thieno[3,2-*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 15. 3-Methyl-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 16. Quinoxaline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 17. Benzo[1,3]dioxole-5-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-115-

18. Quinoline-6-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 19. Furan-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
20. Thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 21. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
22. Furan-3-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 23. Thiophene-3-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
24. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
- 20 25. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
26. 4-Methyl-N-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
27. 4-Methoxy-N-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 28. 4-Isopropyl-N-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
29. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
- 35 30. 4-Imidazol-1-yl-N-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
31. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 40 32. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 45 33. 5-Phenyl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-116-

34. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 5 35. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
36. 4-Difluoromethoxy-N-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 37. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
38. Naphthalene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 39. Quinoline-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
40. Benzo[*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 41. Benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 42. Biphenyl-4-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
43. 4-*tert*-Butyl-N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 44. 4-Dimethylamino-N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
45. 7-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 46. {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
- 40 47. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
48. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 49. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-117-

50. Quinoxaline-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 51. Benzo[1,3]dioxole-5-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
52. Quinoline-6-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 53. Furan-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
54. Thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 55. N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
56. Furan-3-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 57. Thiophene-3-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 58. N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
59. N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 30 60. 4-Methyl-N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
61. 4-Methoxy-N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 62. 4-Isopropyl-N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 40 63. N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
64. 4-Imidazol-1-yl-N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 45 65. N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;

-118-

66. N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 5 67. 5-Phenyl-thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
68. N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 10 69. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
70. 4-Difluoromethoxy-N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 71. N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
72. Naphthalene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 73. Quinoline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
74. Benzo[*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 75. Benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 76. Biphenyl-4-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
77. 4-*tert*-Butyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 78. 4-Dimethylamino-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 40 79. 7-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 80. {3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;

81. 5-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 82. Thieno[3,2-*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 83. 3-Methyl-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 84. Quinoxaline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
85. Benzo[1,3]dioxole-5-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 86. Quinoline-6-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
87. Furan-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 88. Thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
89. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 30 90. Furan-3-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
91. Thiophene-3-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 92. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
93. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 40 94. 4-Methyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 45 95. 4-Methoxy-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

-120-

96. 4-Isopropyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 5 97. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
98. 4-Imidazol-1-yl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 99. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
100. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 15 101. 5-Phenyl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 102. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
103. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 104. 4-Difluoromethoxy-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 105. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
106. Naphthalene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 107. Quinoline-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
108. Benzo[*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 109. Benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 110. Biphenyl-4-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

111. 4-*tert*-Butyl-N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 5 112. 4-Dimethylamino-N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
113. 7-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 114. {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
115. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 116. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
117. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 118. Quinoxaline-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 119. Benzo[1,3]dioxole-5-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
120. Quinoline-6-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 121. Furan-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
122. Thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 123. N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 40 124. Furan-3-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
125. Thiophene-3-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 126. N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;

-122-

127. N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 5 128. 4-Methyl-N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-
pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
129. 4-Methoxy-N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-
pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 130. 4-Isopropyl-N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-
pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
131. N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
- 15 132. 4-Imidazol-1-yl-N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-
pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
133. N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 20 134. N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
135. 5-Phenyl-thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 136. N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 30 137. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-
2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
138. 4-Difluoromethoxy-N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 139. N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 40 140. Naphthalene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-
sulfonyl)hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
141. Quinoline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 142. Benzo[*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-123-

143. Benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 144. Biphenyl-4-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
145. 4-*tert*-Butyl-N-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 146. 4-Dimethylamino-N-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
147. 7-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 148. {3-Methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
149. 5-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 150. Thieno[3,2-*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 151. 3-Methyl-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
152. Quinoxaline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 153. Benzo[1,3]dioxole-5-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 154. Quinoline-6-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
155. Furan-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 156. Thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
157. N-{3-Methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 45 158. Furan-3-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

159. Thiophene-3-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 160. N-{3-Methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
161. N-{3-Methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 10 162. 4-Methyl-N-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
163. 4-Methoxy-N-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 164. 4-Isopropyl-N-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 165. N-{3-Methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
166. 4-Imidazol-1-yl-N-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 167. N-{3-Methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
168. N-{3-Methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 30 169. 5-Phenyl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 170. N-{3-Methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
171. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 172. 4-Difluoromethoxy-N-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 45 173. N-{3-Methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;

-125-

174. Naphthalene-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 175. Quinoline-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
176. Benzo[*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 177. Benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
178. Biphenyl-4-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 179. 4-*tert*-Butyl-N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
180. 4-Dimethylamino-N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 181. 7-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 182. {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
183. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 184. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
185. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 186. Quinoxaline-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 187. Benzo[1,3]dioxole-5-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
188. Quinoline-6-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 189. Furan-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-126-

190. Thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 191. N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
192. Furan-3-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 193. Thiophene-3-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
194. N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
- 15 195. N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
196. 4-Methyl-N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 197. 4-Methoxy-N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 198. 4-Isopropyl-N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
199. N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
- 30 200. 4-Imidazol-1-yl-N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
201. N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 35 202. N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
203. 5-Phenyl-thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 204. N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 45 205. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

206. 4-Difluoromethoxy-N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
207. N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
208. Naphthalene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
209. Quinoline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
210. Benzo[*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
211. Benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
212. Biphenyl-4-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
213. 4-*tert*-Butyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
214. 4-Dimethylamino-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
215. 7-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
216. {3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
217. 5-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
218. Thieno[3,2-*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
219. 3-Methyl-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

220. Quinoxaline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 221. Benzo[1,3]dioxole-5-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 222. Quinoline-6-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
223. Furan-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 224. Thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
225. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 20 226. Furan-3-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
227. Thiophene-3-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 228. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
- 30 229. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 35 230. 4-Methyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
231. 4-Methoxy-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 40 232. 4-Isopropyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
233. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
- 45 234. 4-Imidazol-1-yl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

235. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 5 236. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 10 237. 5-Phenyl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
238. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 15 239. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 240. 4-Difluoromethoxy-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
241. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 25 242. Naphthalene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
243. Quinoline-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 244. Benzo[*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
245. Benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 246. Biphenyl-4-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 247. 4-*tert*-Butyl-N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
248. 4-Dimethylamino-N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 45 249. 7-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-130-

250. {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
- 5 251. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
252. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 253. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
254. Quinoxaline-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 255. Benzo[1,3]dioxole-5-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
256. Quinoline-6-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 257. Furan-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 258. Thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
259. N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 30 260. Furan-3-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
261. Thiophene-3-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 262. N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
263. N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 40 264. 4-Methyl-N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 45 265. 4-Methoxy-N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

-131-

266. 4-Isopropyl-N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 5 267. N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
268. 4-Imidazol-1-yl-N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 269. N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
270. N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 15 271. 5-Phenyl-thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
272. N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 20 273. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 274. 4-Difluoromethoxy-N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
275. N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 30 276. Naphthalene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
277. Quinoline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 278. Benzo[*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 279. Benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
280. Biphenyl-4-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 281. 4-*tert*-Butyl-N-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

-132-

282. 4-Dimethylamino-N-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 5 283. 7-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
284. {3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
- 10 285. 5-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 286. Thieno[3,2-*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
287. 3-Methyl-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 288. Quinoxaline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
289. Benzo[1,3]dioxole-5-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 290. Quinoline-6-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 291. Furan-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
292. Thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 293. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
294. Furan-3-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 295. Thiophene-3-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 296. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
297. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;

-133-

298. 4-Methyl-N-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 5 299. 4-Methoxy-N-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
300. 4-Isopropyl-N-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 301. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
302. 4-Imidazol-1-yl-N-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 303. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 20 304. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
305. 5-Phenyl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 306. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
307. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 308. 4-Difluoromethoxy-N-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 309. N-{3-Methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
310. Naphthalene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 311. Quinoline-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 312. Benzo[*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-134-

313. Benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 314. Biphenyl-4-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
315. 4-*tert*-Butyl-N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 316. 4-Dimethylamino-N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
317. 7-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 318. {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
319. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 320. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 321. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
322. Quinoxaline-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 323. Benzo[1,3]dioxole-5-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
324. Quinoline-6-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 325. Furan-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 326. Thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
327. N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 45 328. Furan-3-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-135-

329. Thiophene-3-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 330. N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
331. N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 10 332. 4-Methyl-N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
333. 4-Methoxy-N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 334. 4-Isopropyl-N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
335. N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
- 20 336. 4-Imidazol-1-yl-N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 337. N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
338. N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 30 339. 5-Phenyl-thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
340. N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 35 341. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 342. 4-Difluoromethoxy-N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
343. N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 45 344. Naphthalene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-136-

345. Quinoline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 346. Benzo[*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
347. Benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 348. Biphenyl-4-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
349. 4-*tert*-Butyl-N-{3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 350. 4-Dimethylamino-N-{3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
351. 7-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 352. {3-Methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
- 25 353. 5-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 354. Thieno[3,2-*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 355. 3-Methyl-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
356. Quinoxaline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 357. Benzo[1,3]dioxole-5-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
358. Quinoline-6-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 359. Furan-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-137-

360. Thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 361. N-{3-Methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
362. Furan-3-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 363. Thiophene-3-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
364. N-{3-Methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
- 15 365. N-{3-Methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
366. 4-Methyl-N-{3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 367. 4-Methoxy-N-{3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 368. 4-Isopropyl-N-{3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
369. N-{3-Methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
- 30 370. 4-Imidazol-1-yl-N-{3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
371. N-{3-Methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 35 372. N-{3-Methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 40 373. 5-Phenyl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
374. N-{3-Methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 45 375. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

376. 4-Difluoromethoxy-N-{3-methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 5 377. N-{3-Methyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
378. Naphthalene-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 379. Quinoline-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
380. Benzo[*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 381. Benzofuran-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 382. Biphenyl-4-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
383. 4-*tert*-Butyl-N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 384. 4-Dimethylamino-N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
385. 7-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 386. {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
- 35 387. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
388. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 389. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
390. Quinoxaline-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 391. Benzo[1,3]dioxole-5-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-139-

392. Quinoline-6-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 393. Furan-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
394. Thiophene-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 395. N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
396. Furan-3-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 397. Thiophene-3-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 398. N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
399. N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 25 400. 4-Methyl-N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
401. 4-Methoxy-N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 402. 4-Isopropyl-N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 403. N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
404. 4-Imidazol-1-yl-N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 40 405. N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
406. N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 45 407. 5-Phenyl-thiophene-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

408. N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 5 409. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
410. 4-Difluoromethoxy-N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 411. N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
412. Naphthalene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 413. Quinoline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 414. Benzo[*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 415. Benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 416. Biphenyl-4-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 417. 4-*tert*-Butyl-N-{3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
418. 4-Dimethylamino-N-{3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 40 419. 7-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 420. {3-Methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;

421. 5-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 422. Thieno[3,2-*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 423. 3-Methyl-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 424. Quinoxaline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 425. Benzo[1,3]dioxole-5-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 426. Quinoline-6-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 427. Furan-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 428. Thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
429. N-{3-Methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 40 430. Furan-3-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
431. Thiophene-3-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 432. N-{3-Methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;

-142-

433. N-{3-Methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 5 434. 4-Methyl-N-{3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
435. 4-Methoxy-N-{3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 436. 4-Isopropyl-N-{3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
437. N-{3-Methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
- 15 438. 4-Imidazol-1-yl-N-{3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 439. N-{3-Methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
440. N-{3-Methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 25 441. 5-Phenyl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 442. N-{3-Methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
443. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 444. 4-Difluoromethoxy-N-{3-methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 40 445. N-{3-Methyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 45 446. Naphthalene-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-143-

447. Quinoline-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 448. Benzo[*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 449. Benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
450. Biphenyl-4-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 451. 4-*tert*-Butyl-N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
452. 4-Dimethylamino-N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 453. 7-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 454. {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
455. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 456. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 457. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 458. Quinoxaline-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 459. Benzo[1,3]dioxole-5-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
460. Quinoline-6-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

461. Furan-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 462. Thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
463. N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 10 464. Furan-3-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
465. Thiophene-3-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 466. N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
- 20 467. N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
468. 4-Methyl-N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 469. 4-Methoxy-N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
470. 4-Isopropyl-N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 471. N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
- 35 472. 4-Imidazol-1-yl-N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
473. N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 40 474. N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 45 475. 5-Phenyl-thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-145-

476. N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 5 477. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
- 10 478. 4-Difluoromethoxy-N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 479. N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 20 480. Naphthalene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-
ylmethanesulfonyl)hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
- 25 481. Quinoline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
- 30 482. Benzo[*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
- 35 483. Benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
- 40 484. Biphenyl-4-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
- 45 485. 4-*tert*-Butyl-N-{3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
486. 4-Dimethylamino-N-{3-methyl-1-[6-oxo-4-(pyridin-3-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
benzamide;
487. 7-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
488. {3-Methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-
pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;

-146-

489. 5-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 490. Thieno[3,2-*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 491. 3-Methyl-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 492. Quinoxaline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 493. Benzo[1,3]dioxole-5-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 494. Quinoline-6-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 495. Furan-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 496. Thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 497. N-{3-Methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 45 498. Furan-3-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
499. Thiophene-3-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
500. N-{3-Methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;

-147-

501. N-{3-Methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 5 502. 4-Methyl-N-{3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
503. 4-Methoxy-N-{3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 504. 4-Isopropyl-N-{3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
505. N-{3-Methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
- 15 506. 4-Imidazol-1-yl-N-{3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
507. N-{3-Methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 20 508. N-{3-Methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 25 509. 5-Phenyl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 510. N-{3-Methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
511. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 512. 4-Difluoromethoxy-N-{3-methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 40 513. N-{3-Methyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 45 514. Naphthalene-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-148-

515. Quinoline-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
516. Benzo[*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
517. Benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
518. Biphenyl-4-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
519. 4-*tert*-Butyl-N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
520. 4-Dimethylamino-N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
521. 7-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
522. {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
523. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
524. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
525. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
526. Quinoxaline-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
527. Benzo[1,3]dioxole-5-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
528. Quinoline-6-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

529. Furan-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 530. Thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
531. N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 10 532. Furan-3-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
533. Thiophene-3-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 534. N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
535. N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 20 536. 4-Methyl-N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 537. 4-Methoxy-N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
538. 4-Isopropyl-N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 539. N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
- 35 540. 4-Imidazol-1-yl-N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
541. N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 40 542. N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
543. 5-Phenyl-thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45

-150-

544. N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 5 545. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
- 10 546. 4-Difluoromethoxy-N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 547. N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
548. Naphthalene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-
ylmethanesulfonyl)hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
- 20 549. Quinoline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
- 25 550. Benzo[*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-
pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-
butyl}-amide;
- 30 551. Benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
- 35 552. Biphenyl-4-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
amide;
553. 4-*tert*-Butyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
benzamide;
- 40 554. 4-Dimethylamino-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
benzamide;
- 45 555. 7-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-
pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-
butyl}-amide;
556. {3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-
pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;

-151-

557. 5-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 558. Thieno[3,2-*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 559. 3-Methyl-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 560. Quinoxaline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 561. Benzo[1,3]dioxole-5-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 562. Quinoline-6-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 563. Furan-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 564. Thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 565. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 45 566. Furan-3-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
567. Thiophene-3-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
568. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;

-152-

569. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 5 570. 4-Methyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 571. 4-Methoxy-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 572. 4-Isopropyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 573. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
- 25 574. 4-Imidazol-1-yl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 575. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 35 576. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 40 577. 5-Phenyl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 578. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
579. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
580. 4-Difluoromethoxy-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
581. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;

-153-

582. Naphthalene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 583. Quinoline-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 584. Benzo[*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 585. Benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 586. Biphenyl-4-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
587. 4-*tert*-Butyl-N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 588. 4-Dimethylamino-N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 589. 7-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 590. {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
591. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 592. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 593. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
594. Quinoxaline-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

595. Benzo[1,3]dioxole-5-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
596. Quinoline-6-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
597. Furan-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
598. Thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
599. N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
600. Furan-3-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
601. Thiophene-3-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
602. N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
603. N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
604. 4-Methyl-N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
605. 4-Methoxy-N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
606. 4-Isopropyl-N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
607. N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;

-155-

608. 4-Imidazol-1-yl-N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 5 609. N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
610. N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 10 611. 5-Phenyl-thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
612. N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
- 15 613. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 614. 4-Difluoromethoxy-N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
615. N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 25 616. Naphthalene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 617. Quinoline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 618. Benzo[*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 619. Benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 620. Biphenyl-4-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-156-

621. 4-*tert*-Butyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 5 622. 4-Dimethylamino-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 623. 7-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 624. {3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
625. 5-Methoxy-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 626. Thieno[3,2-*b*]thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 627. 3-Methyl-benzofuran-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 628. Quinoxaline-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 629. Benzo[1,3]dioxole-5-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 630. Quinoline-6-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 631. Furan-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
632. Thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-157-

633. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
- 5 634. Furan-3-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 635. Thiophene-3-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
636. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
- 15 637. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 20 638. 4-Methyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
639. 4-Methoxy-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 640. 4-Isopropyl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 641. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
642. 4-Imidazol-1-yl-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 643. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 40 644. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
645. 5-Phenyl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 646. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;

-158-

- 5 647. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
648. 4-Difluoromethoxy-N-{3-methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 649. N-{3-Methyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 15 650. Naphthalene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 651. Quinoline-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 652. Benzo[*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 653. Benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 654. Biphenyl-4-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
655. 4-*tert*-Butyl-N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 40 656. 4-Dimethylamino-N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 45 657. 7-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
658. {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-carbamic acid benzyl ester;
659. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-159-

- 5 660. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
661. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 662. Quinoxaline-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 663. Benzo[1,3]dioxole-5-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 664. Quinoline-6-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 665. Furan-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 666. Thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 667. N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethyl-benzamide;
668. Furan-3-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 669. Thiophene-3-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 670. N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-phenoxy-benzamide;
671. N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;

-160-

672. 4-Methyl-N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 5 673. 4-Methoxy-N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
674. 4-Isopropyl-N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 675. N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-vinyl-benzamide;
676. 4-Imidazol-1-yl-N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 677. N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
678. N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-oxazol-5-yl-benzamide;
- 20 679. 5-Phenyl-thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 680. N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-trifluoromethoxy-benzamide;
681. 5-Pyridin-2-yl-thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 682. 4-Difluoromethoxy-N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 683. N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
684. 4-*tert*-Butyl-N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-benzamide;
- 40 685. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 45 686. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;

-161-

687. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 5 688. N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-phenoxy-benzamide;
689. N-{1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-thiophen-2-yl-benzamide;
- 10 690. 4-*tert*-Butyl-N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
691. 5-Methoxy-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 15 692. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 20 693. 3-Methyl-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 25 694. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-phenoxy-benzamide;
695. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-thiophen-2-yl-benzamide;
- 30 696. 4-*tert*-Butyl-N-{2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-benzamide;
697. 5-Methoxy-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 35 698. Thieno[3,2-*b*]thiophene-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 40 699. 3-Methyl-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 45 700. N-{2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-phenoxy-benzamide;

-162-

701. N-{2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-thiophen-2-yl-benzamide;
- 5 702. 4-*tert*-Butyl-N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrole-1-carbonyl]-cyclohexyl}-benzamide;
703. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 10 704. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
705. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-3-sulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 15 706. N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-
carbonyl]-cyclohexyl}-4-phenoxy-benzamide;
707. N-{1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-
carbonyl]-cyclohexyl}-4-thiophen-2-yl-benzamide;
- 20 708. 4-*tert*-Butyl-N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-3-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 25 709. 5-Methoxy-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-
[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-
amide;
- 30 710. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-
[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-
amide;
711. 3-Methyl-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-
oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-
amide;
- 35 712. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-phenoxy-benzamide;
- 40 713. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-thiophen-2-yl-benzamide;
714. 4-*tert*-Butyl-N-{2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-
pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-benzamide;
- 45 715. 5-Methoxy-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridine-3-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-
amide;

-163-

716. Thieno[3,2-*b*]thiophene-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 5 717. 3-Methyl-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 10 718. N-{2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-phenoxy-benzamide;
- 15 719. N-{2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-thiophen-2-yl-benzamide;
- 20 720. 4-*tert*-Butyl-N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-benzamide;
721. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 25 722. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 30 723. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
724. N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-phenoxy-benzamide;
- 35 725. N-{1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-thiophen-2-yl-benzamide;
726. 4-*tert*-Butyl-N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 40 727. 5-Methoxy-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 45 728. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
729. 3-Methyl-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;

-164-

730. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-phenoxy-benzamide;
- 5 731. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-thiophen-2-yl-benzamide;
732. 4-*tert*-Butyl-N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-benzamide;
- 10 733. 5-Methoxy-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 15 734. Thieno[3,2-*b*]thiophene-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 20 735. 3-Methyl-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
736. N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-phenoxy-benzamide;
- 25 737. N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-thiophen-2-yl-benzamide;
738. 4-*tert*-Butyl-N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-benzamide;
- 30 739. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 35 740. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
741. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 40 742. N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-phenoxy-benzamide;
743. N-{1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-thiophen-2-yl-benzamide;
- 45 744. 4-*tert*-Butyl-N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;

-165-

745. 5-Methoxy-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 5 746. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 10 747. 3-Methyl-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 15 748. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-phenoxy-benzamide;
- 20 749. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-thiophen-2-yl-benzamide;
- 25 750. 4-*tert*-Butyl-N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-benzamide;
- 30 751. 5-Methoxy-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 35 752. Thieno[3,2-*b*]thiophene-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 40 753. 3-Methyl-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 45 754. N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-phenoxy-benzamide;
755. N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-thiophen-2-yl-benzamide;
756. 4-*tert*-Butyl-N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-benzamide;
757. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
758. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;

-166-

759. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 5 760. N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-phenoxy-benzamide;
761. N-{1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-thiophen-2-yl-benzamide;
- 10 762. 4-*tert*-Butyl-N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
763. 5-Methoxy-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 15 764. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 20 765. 3-Methyl-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 25 766. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-phenoxy-benzamide;
767. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-thiophen-2-yl-benzamide;
- 30 768. 4-*tert*-Butyl-N-{2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-benzamide;
769. 5-Methoxy-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 35 770. Thieno[3,2-*b*]thiophene-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 40 771. 3-Methyl-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 45 772. N-{2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-phenoxy-benzamide;

-167-

773. N-{2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-thiophen-2-yl-benzamide;
- 5 774. 4-*tert*-Butyl-N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-
pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-benzamide;
775. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-
acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 10 776. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-
acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
777. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(2-pyridin-3-yl-
acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 15 778. N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-
carbonyl]-cyclohexyl}-4-phenoxy-benzamide;
779. N-{1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-
20 carbonyl]-cyclohexyl}-4-thiophen-2-yl-benzamide;
780. 4-*tert*-Butyl-N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-
acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 25 781. 5-Methoxy-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-
[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-
amide;
782. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-
30 [6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-
amide;
783. 3-Methyl-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-
oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-
35 amide;
784. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-phenoxy-benzamide;
- 40 785. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-thiophen-2-yl-benzamide;
786. 4-*tert*-Butyl-N-{2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-
pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-benzamide;
- 45 787. 5-Methoxy-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(2-pyridin-3-
yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-
ethyl}-amide;

-168-

788. Thieno[3,2-*b*]thiophene-2-carboxylic acid {2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 5 789. 3-Methyl-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 10 790. N-{2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-phenoxy-benzamide;
791. N-{2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-thiophen-2-yl-benzamide;
- 15 792. 4-*tert*-Butyl-N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-benzamide;
793. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 20 794. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 25 795. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 30 796. N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-phenoxy-benzamide;
797. N-{1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-thiophen-2-yl-benzamide;
- 35 798. 4-*tert*-Butyl-N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 40 799. 5-Methoxy-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 45 800. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;

-169-

801. 3-Methyl-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 5 802. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-phenoxybenzamide;
- 10 803. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-thiophen-2-yl-benzamide;
- 15 804. 4-*tert*-Butyl-N-{2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-benzamide;
- 20 805. 5-Methoxy-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 25 806. Thieno[3,2-*b*]thiophene-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 30 807. 3-Methyl-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 35 808. N-{2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-phenoxybenzamide;
- 40 809. N-{2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-thiophen-2-ylbenzamide;
- 45 810. 4-*tert*-Butyl-N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-benzamide;
811. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
812. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;

-170-

813. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 5 814. N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-phenoxy-benzamide;
815. N-{1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-thiophen-2-yl-benzamide;
- 10 816. 4-*tert*-Butyl-N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
817. 5-Methoxy-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 15 818. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 20 819. 3-Methyl-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 25 820. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-phenoxy-benzamide;
- 30 821. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-thiophen-2-yl-benzamide;
- 35 822. 4-*tert*-Butyl-N-{2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-benzamide;
- 40 823. 5-Methoxy-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 45 824. Thieno[3,2-*b*]thiophene-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
825. 3-Methyl-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;

-171-

826. N-{2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-phenoxy-benzamide;
827. N-{2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-thiophen-2-yl-benzamide;
828. 4-*tert*-Butyl-N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-benzamide;
829. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
830. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
831. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
832. N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-phenoxy-benzamide;
833. N-{1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-thiophen-2-yl-benzamide;
834. 4-*tert*-Butyl-N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
835. 5-Methoxy-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
836. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
837. 3-Methyl-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
838. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-phenoxy-benzamide;

-172-

839. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-thiophen-2-yl-benzamide;
- 5 840. 4-*tert*-Butyl-N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-benzamide;
- 10 841. 5-Methoxy-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 15 842. Thieno[3,2-*b*]thiophene-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 20 843. 3-Methyl-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 25 844. N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-phenoxy-benzamide;
- 30 845. N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-thiophen-2-yl-benzamide;
- 35 846. 4-*tert*-Butyl-N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-benzamide;
- 40 847. 5-Methoxy-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
- 45 848. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
849. 3-Methyl-benzofuran-2-carboxylic acid {1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-amide;
850. N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-phenoxy-benzamide;

-173-

851. N-{1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-cyclohexyl}-4-thiophen-2-yl-benzamide;
- 5 852. 4-*tert*-Butyl-N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 10 853. 5-Methoxy-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
854. Thieno[3,2-*b*]thiophene-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 15 855. 3-Methyl-benzofuran-2-carboxylic acid {1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 20 856. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-phenoxy-benzamide;
- 25 857. N-{1-cyclopropylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-4-thiophen-2-yl-benzamide;
858. 4-*tert*-Butyl-N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-benzamide;
- 30 859. 5-Methoxy-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 35 860. Thieno[3,2-*b*]thiophene-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 40 861. 3-Methyl-benzofuran-2-carboxylic acid {2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-amide;
- 45 862. N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-phenoxy-benzamide;

-174-

863. N-{2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-4-thiophen-2-yl-benzamide;
- 5 864. 2-Isobutyl-4-morpholin-4-yl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
865. 2-Isobutyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-piperazin-1-yl-butane-1,4-dione;
- 10 866. 2-Isobutyl-4-(4-methyl-piperazin-1-yl)-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
867. 2-Isobutyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(4-phenyl-piperazin-1-yl)-butane-1,4-dione;
- 15 868. 2-Isobutyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(3,4,4a,8a-tetrahydro-1H-isoquinolin-2-yl)-butane-1,4-dione;
- 20 869. 2-Isobutyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(1,3,3a,7a-tetrahydro-isoindol-2-yl)-butane-1,4-dione;
870. 4-(4-Benzyl-piperazin-1-yl)-2-isobutyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 25 871. 2-Isobutyl-4-morpholin-4-yl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
872. 2-Isobutyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-piperazin-1-yl-butane-1,4-dione;
- 30 873. 2-Isobutyl-4-(4-methyl-piperazin-1-yl)-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 35 874. 2-Isobutyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(4-phenyl-piperazin-1-yl)-butane-1,4-dione;
875. 2-Isobutyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(3,4,4a,8a-tetrahydro-1H-isoquinolin-2-yl)-butane-1,4-dione;
- 40 876. 2-Isobutyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(1,3,3a,7a-tetrahydro-isoindol-2-yl)-butane-1,4-dione;
877. 4-(4-Benzyl-piperazin-1-yl)-2-isobutyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 45 878. 2-Isobutyl-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;

-175-

879. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-piperazin-1-yl-butane-1,4-dione;
- 5 880. 2-Isobutyl-4-(4-methyl-piperazin-1-yl)-1-[6-oxo-4-(1-oxy-pyridine-2-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
881. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(4-phenyl-piperazin-1-yl)-butane-1,4-dione;
- 10 882. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(3,4,4a,8a-tetrahydro-1H-isoquinolin-2-yl)-butane-1,4-dione;
883. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(1,3,3a,7a-tetrahydro-isoindol-2-yl)-butane-1,4-dione;
- 15 884. 4-(4-Benzyl-piperazin-1-yl)-2-isobutyl-1-[6-oxo-4-(1-oxy-pyridine-2-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 20 885. 2-Isobutyl-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
886. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-piperazin-1-yl-butane-1,4-dione;
- 25 887. 2-Isobutyl-4-(4-methyl-piperazin-1-yl)-1-[6-oxo-4-(1-oxy-pyridine-3-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
888. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(4-phenyl-piperazin-1-yl)-butane-1,4-dione;
- 30 889. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(3,4,4a,8a-tetrahydro-1H-isoquinolin-2-yl)-butane-1,4-dione;
890. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(1,3,3a,7a-tetrahydro-isoindol-2-yl)-butane-1,4-dione;
- 35 891. 4-(4-Benzyl-piperazin-1-yl)-2-isobutyl-1-[6-oxo-4-(1-oxy-pyridine-3-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 40 892. 2-Isobutyl-4-morpholin-4-yl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-
pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
893. 2-Isobutyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-piperazin-1-yl-butane-1,4-dione;
- 45 894. 2-Isobutyl-4-(4-methyl-piperazin-1-yl)-1-[6-oxo-4-(pyridine-2-carbonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;

895. 2-Isobutyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(4-phenyl-piperazin-1-yl)-butane-1,4-dione;
- 5 896. 2-Isobutyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(3,4,4a,8a-tetrahydro-1H-isoquinolin-2-yl)-butane-1,4-dione;
897. 2-Isobutyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(1,3,3a,7a-tetrahydro-isoindol-2-yl)-butane-1,4-dione;
- 10 898. 4-(4-Benzyl-piperazin-1-yl)-2-isobutyl-1-[6-oxo-4-(pyridine-2-carbonyl)-
hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-butane-1,4-dione;
899. 2-Isobutyl-4-morpholin-4-yl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-
hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-butane-1,4-dione;
- 15 900. 2-Isobutyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-piperazin-1-yl-butane-1,4-dione;
901. 2-Isobutyl-4-(4-methyl-piperazin-1-yl)-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-
hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-butane-1,4-dione;
- 20 902. 2-Isobutyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(4-phenyl-piperazin-1-yl)-butane-1,4-dione;
- 25 903. 2-Isobutyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(3,4,4a,8a-tetrahydro-1H-isoquinolin-2-yl)-butane-1,4-dione;
904. 2-Isobutyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-4-(1,3,3a,7a-tetrahydro-isoindol-2-yl)-butane-1,4-dione;
- 30 905. 4-(4-Benzyl-piperazin-1-yl)-2-isobutyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-
hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-butane-1,4-dione;
- 35 906. 2-Isobutyl-4-morpholin-4-yl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-
hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-butane-1,4-dione;
907. 2-Isobutyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-
pyrrolo[3,2-b]pyrrol-1-yl]-4-piperazin-1-yl-butane-1,4-dione;
- 40 908. 2-Isobutyl-4-(4-methyl-piperazin-1-yl)-1-[6-oxo-4-(pyridin-2-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-butane-1,4-dione;
909. 2-Isobutyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-
pyrrolo[3,2-b]pyrrol-1-yl]-4-(4-phenyl-piperazin-1-yl)-butane-1,4-dione;
- 45

-177-

910. 2-Isobutyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(3,4,4a,8a-tetrahydro-1H-isoquinolin-2-yl)-butane-1,4-dione;
- 5 911. 2-Isobutyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(1,3,3a,7a-tetrahydro-isoindol-2-yl)-butane-1,4-dione;
- 10 912. 4-(4-Benzyl-piperazin-1-yl)-2-isobutyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
913. 2-Isobutyl-4-morpholin-4-yl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 15 914. 2-Isobutyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-piperazin-1-yl-butane-1,4-dione;
915. 2-Isobutyl-4-(4-methyl-piperazin-1-yl)-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 20 916. 2-Isobutyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(4-phenyl-piperazin-1-yl)-butane-1,4-dione;
- 25 917. 2-Isobutyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(3,4,4a,8a-tetrahydro-1H-isoquinolin-2-yl)-butane-1,4-dione;
- 30 918. 2-Isobutyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(1,3,3a,7a-tetrahydro-isoindol-2-yl)-butane-1,4-dione;
- 35 919. 4-(4-Benzyl-piperazin-1-yl)-2-isobutyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
920. 2-Isobutyl-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 40 921. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-piperazin-1-yl-butane-1,4-dione;
922. 2-Isobutyl-4-(4-methyl-piperazin-1-yl)-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 45 923. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(4-phenyl-piperazin-1-yl)-butane-1,4-dione;

-178-

924. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(3,4,4a,8a-tetrahydro-1H-isoquinolin-2-yl)-butane-1,4-dione;
- 5 925. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(1,3,3a,7a-tetrahydro-isoindol-2-yl)-butane-1,4-dione;
- 10 926. 4-(4-Benzyl-piperazin-1-yl)-2-isobutyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
927. 2-Isobutyl-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 15 928. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-piperazin-1-yl-butane-1,4-dione;
929. 2-Isobutyl-4-(4-methyl-piperazin-1-yl)-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 20 930. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(4-phenyl-piperazin-1-yl)-butane-1,4-dione;
931. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(3,4,4a,8a-tetrahydro-1H-isoquinolin-2-yl)-butane-1,4-dione;
- 25 932. 2-Isobutyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-4-(1,3,3a,7a-tetrahydro-isoindol-2-yl)-butane-1,4-dione;
- 30 933. 4-(4-Benzyl-piperazin-1-yl)-2-isobutyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 35 934. 4-(2-Biphenyl-3-yl-4-methyl-pentanoyl)-1-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
935. 4-(2-Biphenyl-3-yl-4-methyl-pentanoyl)-1-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 40 936. 4-(2-Biphenyl-3-yl-4-methyl-pentanoyl)-1-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
937. 4-(2-Biphenyl-3-yl-4-methyl-pentanoyl)-1-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 45 938. 4-(2-Biphenyl-3-yl-4-methyl-pentanoyl)-1-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;

939. 4-(2-Biphenyl-3-yl-4-methyl-pentanoyl)-1-(2-pyridin-3-yl-acetyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 5 940. 4-(2-Biphenyl-3-yl-4-methyl-pentanoyl)-1-(pyridin-2-ylmethanesulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
941. 4-(2-Biphenyl-3-yl-4-methyl-pentanoyl)-1-(pyridin-3-ylmethanesulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 10 942. 4-(2-Biphenyl-3-yl-4-methyl-pentanoyl)-1-(1-oxy-pyridin-2-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
943. 4-(2-Biphenyl-3-yl-4-methyl-pentanoyl)-1-(1-oxy-pyridin-3-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 15 944. 4-[4-Methyl-2-(3-pyridin-2-yl-phenyl)-pentanoyl]-1-(pyridine-2-sulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 20 945. 4-[4-Methyl-2-(3-pyridin-2-yl-phenyl)-pentanoyl]-1-(pyridine-3-sulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
946. 4-[4-Methyl-2-(3-pyridin-2-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridine-2-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 25 947. 4-[4-Methyl-2-(3-pyridin-2-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridine-3-
sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
948. 4-[4-Methyl-2-(3-pyridin-2-yl-phenyl)-pentanoyl]-1-(pyridine-2-
carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 30 949. 4-[4-Methyl-2-(3-pyridin-2-yl-phenyl)-pentanoyl]-1-(2-pyridin-3-yl-
acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 35 950. 4-[4-Methyl-2-(3-pyridin-2-yl-phenyl)-pentanoyl]-1-(pyridin-2-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
951. 4-[4-Methyl-2-(3-pyridin-2-yl-phenyl)-pentanoyl]-1-(pyridin-3-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 40 952. 4-[4-Methyl-2-(3-pyridin-2-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridin-2-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
953. 4-[4-Methyl-2-(3-pyridin-2-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridin-3-
ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 45 954. 4-[4-Methyl-2-(3-pyridin-3-yl-phenyl)-pentanoyl]-1-(pyridine-2-sulfonyl)-
hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;

955. 4-[4-Methyl-2-(3-pyridin-3-yl-phenyl)-pentanoyl]-1-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 5 956. 4-[4-Methyl-2-(3-pyridin-3-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
957. 4-[4-Methyl-2-(3-pyridin-3-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 10 958. 4-[4-Methyl-2-(3-pyridin-3-yl-phenyl)-pentanoyl]-1-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
959. 4-[4-Methyl-2-(3-pyridin-3-yl-phenyl)-pentanoyl]-1-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 15 960. 4-[4-Methyl-2-(3-pyridin-3-yl-phenyl)-pentanoyl]-1-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
961. 4-[4-Methyl-2-(3-pyridin-3-yl-phenyl)-pentanoyl]-1-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 20 962. 4-[4-Methyl-2-(3-pyridin-3-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 25 963. 4-[4-Methyl-2-(3-pyridin-3-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
964. 4-[4-Methyl-2-(3-pyridin-4-yl-phenyl)-pentanoyl]-1-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 30 965. 4-[4-Methyl-2-(3-pyridin-4-yl-phenyl)-pentanoyl]-1-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 35 966. 4-[4-Methyl-2-(3-pyridin-4-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
967. 4-[4-Methyl-2-(3-pyridin-4-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 40 968. 4-[4-Methyl-2-(3-pyridin-4-yl-phenyl)-pentanoyl]-1-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
969. 4-[4-Methyl-2-(3-pyridin-4-yl-phenyl)-pentanoyl]-1-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 45 970. 4-[4-Methyl-2-(3-pyridin-4-yl-phenyl)-pentanoyl]-1-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;

971. 4-[4-Methyl-2-(3-pyridin-4-yl-phenyl)-pentanoyl]-1-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
- 5 972. 4-[4-Methyl-2-(3-pyridin-4-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one;
973. 4-[4-Methyl-2-(3-pyridin-4-yl-phenyl)-pentanoyl]-1-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-3-one.

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Other compounds of the invention include, but are not limited to, the following examples where all 4 stereoisomeric combinations of the bicyclic ketone are included where P₂ is CH₂, i.e. (3a*S*, 6a*S*), (3a*R*, 6a*S*), (3a*S*, 6a*R*), (3a*R*, 6a*R*) and also included are the equivalent analogues where P₂ is O and NH. More preferred compounds consist of the cis-bicyclic isomers which, when P₂ is CH₂, are designated as (3a*R*, 6a*S*) and (3a*S*, 6a*R*) and also more preferred are the equivalent cis-bicyclic analogues where P₂ is O and NH.

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974. Furan-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
975. Thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
976. Benzo[*b*]thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
977. Furan-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
978. Thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
979. Benzo[*b*]thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
980. Naphthalene-1-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
981. Quinoline-8-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;

-182-

982. 4-*tert*-Butyl-N-{1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 5 983. 4-*tert*-Butyl-N-{1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
984. 4-*tert*-Butyl-N-{1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 10 985. 4-*tert*-Butyl-N-{1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
986. Biphenyl-4-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 15 987. Biphenyl-4-carboxylic acid {1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
988. Biphenyl-4-carboxylic acid {1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 20 989. Biphenyl-4-carboxylic acid {1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
990. Furan-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 991. Thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 992. Benzo[*b*]thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
993. Furan-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 35 994. Thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 40 995. Benzo[*b*]thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 45 996. Naphthalene-1-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
997. Quinoline-8-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;

998. 4-*tert*-Butyl-N-{1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 5 999. 4-*tert*-Butyl-N-{1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1000. 4-*tert*-Butyl-N-{1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 10 1001. 4-*tert*-Butyl-N-{1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1002. Biphenyl-4-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 15 1003. Biphenyl-4-carboxylic acid {1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1004. Biphenyl-4-carboxylic acid {1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 20 1005. Biphenyl-4-carboxylic acid {1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 25 1006. Furan-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1007. Thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 1008. Benzo[*b*]thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 1009. Furan-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1010. Thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 40 1011. Benzo[*b*]thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 45 1012. Naphthalene-1-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;

1013. Quinoline-8-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 5 1014. 4-*tert*-Butyl-N-{1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1015. 4-*tert*-Butyl-N-{1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 10 1016. 4-*tert*-Butyl-N-{1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1017. 4-*tert*-Butyl-N-{1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 15 1018. Biphenyl-4-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 20 1019. Biphenyl-4-carboxylic acid {1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1020. Biphenyl-4-carboxylic acid {1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 25 1021. Biphenyl-4-carboxylic acid {1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1022. Furan-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 1023. Thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 1024. Benzo[*b*]thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1025. Furan-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 40 1026. Thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 45 1027. Benzo[*b*]thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;

-185-

1028. Naphthalene-1-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 5 1029. Quinoline-8-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1030. 4-*tert*-Butyl-N-{1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 10 1031. 4-*tert*-Butyl-N-{1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1032. 4-*tert*-Butyl-N-{1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 15 1033. 4-*tert*-Butyl-N-{1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 20 1034. Biphenyl-4-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1035. Biphenyl-4-carboxylic acid {1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 25 1036. Biphenyl-4-carboxylic acid {1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1037. Biphenyl-4-carboxylic acid {1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 30 1038. Furan-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 1039. Thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1040. Benzo[*b*]thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 1041. Furan-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 45 1042. Thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;

1043. Benzo[b]thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 5 1044. Naphthalene-1-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1045. Quinoline-8-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 10 1046. 4-*tert*-Butyl-N-{1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1047. 4-*tert*-Butyl-N-{1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 15 1048. 4-*tert*-Butyl-N-{1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 20 1049. 4-*tert*-Butyl-N-{1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1050. Biphenyl-4-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 25 1051. Biphenyl-4-carboxylic acid {1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1052. Biphenyl-4-carboxylic acid {1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 30 1053. Biphenyl-4-carboxylic acid {1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 35 1054. Furan-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1055. Thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 1056. Benzo[b]thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 1057. Furan-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;

-187-

1058. Thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 5 1059. Benzo[*b*]thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 10 1060. Naphthalene-1-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1061. Quinoline-8-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 15 1062. 4-*tert*-Butyl-N-{1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1063. 4-*tert*-Butyl-N-{1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 20 1064. 4-*tert*-Butyl-N-{1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1065. 4-*tert*-Butyl-N-{1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 25 1066. Biphenyl-4-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1067. Biphenyl-4-carboxylic acid {1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 30 1068. Biphenyl-4-carboxylic acid {1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 35 1069. Biphenyl-4-carboxylic acid {1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1070. Furan-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 1071. Thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 1072. Benzo[*b*]thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-188-

1073. Furan-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 5 1074. Thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 10 1075. Benzo[*b*]thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 15 1076. Naphthalene-1-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 20 1077. Quinoline-8-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 25 1078. 4-*tert*-Butyl-N-{1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1079. 4-*tert*-Butyl-N-{1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 30 1080. 4-*tert*-Butyl-N-{1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1081. 4-*tert*-Butyl-N-{1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 35 1082. Biphenyl-4-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 40 1083. Biphenyl-4-carboxylic acid {1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1084. Biphenyl-4-carboxylic acid {1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 45 1085. Biphenyl-4-carboxylic acid {1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;

-189-

1086. Furan-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 1087. Thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 1088. Benzo[*b*]thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 1089. Furan-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 20 1090. Thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 25 1091. Benzo[*b*]thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 30 1092. Naphthalene-1-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 35 1093. Quinoline-8-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 40 1094. 4-*tert*-Butyl-N-{1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 45 1095. 4-*tert*-Butyl-N-{1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1096. 4-*tert*-Butyl-N-{1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1097. 4-*tert*-Butyl-N-{1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
1098. Biphenyl-4-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;

-190-

1099. Biphenyl-4-carboxylic acid {1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 5 1100. Biphenyl-4-carboxylic acid {1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 10 1101. Biphenyl-4-carboxylic acid {1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 15 1102. Furan-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 1103. Thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 1104. Benzo[*b*]thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 1105. Furan-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 35 1106. Thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 40 1107. Benzo[*b*]thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 45 1108. Naphthalene-1-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1109. Quinoline-8-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1110. 4-*tert*-Butyl-N-{1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;

-191-

1111. 4-*tert*-Butyl-N-{1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 5 1112. 4-*tert*-Butyl-N-{1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 10 1113. 4-*tert*-Butyl-N-{1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 15 1114. Biphenyl-4-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 20 1115. Biphenyl-4-carboxylic acid {1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 25 1116. Biphenyl-4-carboxylic acid {1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 30 1117. Biphenyl-4-carboxylic acid {1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 35 1118. Furan-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 1119. Thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 45 1120. Benzo[*b*]thiophene-3-carboxylic acid {3,3-dimethyl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1121. Furan-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1122. Thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;

-192-

1123. Benzo[b]thiophene-3-carboxylic acid {1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 5 1124. Naphthalene-1-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 10 1125. Quinoline-8-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 15 1126. 4-*tert*-Butyl-N-{1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 20 1127. 4-*tert*-Butyl-N-{1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 25 1128. 4-*tert*-Butyl-N-{1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 30 1129. 4-*tert*-Butyl-N-{1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide;
- 35 1130. Biphenyl-4-carboxylic acid {1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 40 1131. Biphenyl-4-carboxylic acid {1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
- 45 1132. Biphenyl-4-carboxylic acid {1-(4-methoxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1133. Biphenyl-4-carboxylic acid {1-(3-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-amide;
1134. 2-Cyclohexylmethyl-4-morpholin-4-yl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
1135. 2-Cyclohexylmethyl-4-morpholin-4-yl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;

-193-

1136. 2-Cyclohexylmethyl-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 5 1137. 2-Cyclohexylmethyl-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
1138. 2-Cyclohexylmethyl-4-morpholin-4-yl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 10 1139. 2-Cyclohexylmethyl-4-morpholin-4-yl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
1140. 2-Cyclohexylmethyl-4-morpholin-4-yl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 15 1141. 2-Cyclohexylmethyl-4-morpholin-4-yl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
1142. 2-Cyclohexylmethyl-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 20 1143. 2-Cyclohexylmethyl-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 25 1144. 2-(2,2-Dimethyl-propyl)-4-morpholin-4-yl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
1145. 2-(2,2-Dimethyl-propyl)-4-morpholin-4-yl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 30 1146. 2-(2,2-Dimethyl-propyl)-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
1147. 2-(2,2-Dimethyl-propyl)-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 35 1148. 2-(2,2-Dimethyl-propyl)-4-morpholin-4-yl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 40 1149. 2-(2,2-Dimethyl-propyl)-4-morpholin-4-yl-1-[6-oxo-4-(2-pyridin-3-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
1150. 2-(2,2-Dimethyl-propyl)-4-morpholin-4-yl-1-[6-oxo-4-(pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;
- 45 1151. 2-(2,2-Dimethyl-propyl)-4-morpholin-4-yl-1-[6-oxo-4-(pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;

-194-

1152. 2-(2,2-Dimethyl-propyl)-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridin-2-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione;

5 1153. 2-(2,2-Dimethyl-propyl)-4-morpholin-4-yl-1-[6-oxo-4-(1-oxy-pyridin-3-ylmethanesulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-butane-1,4-dione.

Additional compounds of the invention include, but are not limited to, the following examples where all 4 stereoisomeric combinations of the bicyclic ketone are included where P₂ is CH₂, i.e. (3a*S*, 6a*S*), (3a*R*, 6a*S*), (3a*S*, 6a*R*), (3a*R*, 6a*R*) and also included are the equivalent analogues where P₂ is O and NH. More preferred compounds consist of the cis-bicyclic isomers which, when P₂ is CH₂, are designated as (3a*R*, 6a*S*) and (3a*S*, 6a*R*) and also more preferred are the equivalent cis-bicyclic analogues where P₂ is O and NH.

15

1154. *N*-[1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-*tert*-butylbenzamide;

20 1155. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

1156. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

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1157. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

30 1158. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

1159. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

35 1160. *N*-[1-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-*tert*-butylbenzamide;

1161. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

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1162. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

-195-

1163. 4-*tert*-Butyl-*N*-[3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-benzamide;
- 5 1164. 4-[2-(4-*tert*-Butyl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide;
1165. 4-[2-(4-*tert*-Butyl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl-amide;
- 10 1166. 4-[2-(4-*tert*-Butyl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenyl ester;
1167. 4-[2-(4-*tert*-Butyl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl ester;
- 15 1168. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1169. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(piperidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 1170. 4-*tert*-Butyl-*N*-{3-methyl-1-[4-(morpholine-4-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1171. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(piperazine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 1172. 4-*tert*-Butyl-*N*-{3-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 1173. 4-*tert*-Butyl-*N*-(3-methyl-1-{4-[2-(4-methyl-piperazin-1-yl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-butyl)-benzamide;
1174. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(2-piperazin-1-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 1175. 4-*tert*-Butyl-*N*-{1-[4-(furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1176. 4-*tert*-Butyl-*N*-{1-[4-(5-chloro-furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 40 1177. 4-*tert*-Butyl-*N*-{1-[4-(thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 45 1178. 4-*tert*-Butyl-*N*-{1-[4-(5-chloro-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

-196-

1179. 4-*tert*-Butyl-*N*-{1-[4-(furan-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 5 1180. 4-*tert*-Butyl-*N*-{1-[4-(thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1181. 4-*tert*-Butyl-*N*-[1-(4-cyclopentanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide;
- 10 1182. 4-*tert*-Butyl-*N*-[1-(4-cyclohexanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide;
1183. 4-*tert*-Butyl-*N*-{1-[4-(cyclopent-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 15 1184. 4-*tert*-Butyl-*N*-{1-[4-(2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1185. 4-*tert*-Butyl-*N*-{1-[4-(2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 20 1186. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1187. *N*-{1-[4-(1-Acetyl-pyrrolidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 25 1188. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(piperidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 1189. *N*-{1-[4-(1-Acetyl-piperidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1190. 4-*tert*-Butyl-*N*-{3-methyl-1-[6-oxo-4-(tetrahydro-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 1191. *N*-{1-[4-(1-Amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1192. *N*-{1-[4-(1-Amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 40 1193. *N*-{1-[4-(1-Amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 45 1194. *N*-{1-[4-(1-Acetylamino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;

-197-

1195. *N*-{1-[4-(1-Acetylamino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 5 1196. *N*-{1-[4-(1-Acetylamino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1197. 4-*tert*-Butyl-*N*-{1-[4-(1-hydroxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 10 1198. 4-*tert*-Butyl-*N*-{1-[4-(1-hydroxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1199. 4-*tert*-Butyl-*N*-{1-[4-(1-hydroxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 15 1200. 4-*tert*-Butyl-*N*-{1-[4-(1-methoxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1201. 4-*tert*-Butyl-*N*-{1-[4-(1-methoxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 20 1202. 4-*tert*-Butyl-*N*-{1-[4-(1-methoxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1203. *N*-{1-[4-(2-Amino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 25 1204. *N*-{1-[4-(2-Amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 30 1205. *N*-{1-[4-(2-Acetylamino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1206. *N*-{1-[4-(2-Acetylamino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 35 1207. *N*-{1-[4-(2-Acetylamino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1208. *N*-{1-[4-(2-Acetylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 40 1209. *N*-(1-[4-[2-(Acetyl-methyl-amino)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl)-4-*tert*-butyl-benzamide;
- 45 1210. 4-*tert*-Butyl-*N*-{1-[4-(2-dimethylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

-198-

1211. *N*-{1-[4-(2-Amino-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 5 1212. *N*-{1-[4-(2-Acetylamino-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1213. *N*-{1-[4-(2-amino-3-methyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 10 1214. *N*-{1-[4-(2-Acetylamino-3-methyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1215. *N*-{1-[4-(2-amino-3,3-dimethyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 15 1216. *N*-{1-[4-(2-Acetylamino-3,3-dimethyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1217. *N*-{1-[4-(2-Amino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 20 1218. *N*-{1-[4-(2-Acetylamino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1219. 4-*tert*-Butyl-*N*-[3-methyl-1-(6-oxo-4-pentanoyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-benzamide;
- 25 1220. 4-*tert*-Butyl-*N*-{3-methyl-1-[4-(3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 1221. 4-*tert*-Butyl-*N*-{3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1222. *N*-{1-[4-(2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 35 1223. *N*-{1-[4-(2-Acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1224. *N*-{1-[4-(2-Amino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 40 1225. *N*-{1-[4-(2-Acetylamino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 45 1226. *N*-{1-[4-(2-Amino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;

1227. *N*-{1-[4-(2-Acetylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 5 1228. *N*-{1-[4-(2-Amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1229. *N*-{1-[4-(2-Acetylamino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 10 1230. *N*-{1-[4-(2-hydroxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
1231. *N*-{1-[4-(2-methoxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide;
- 15 1232. 4-*tert*-Butyl-*N*-{1-[4-(2-hydroxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1233. 4-*tert*-Butyl-*N*-{1-[4-(2-methoxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 20 1234. 4-*tert*-Butyl-*N*-{1-[4-(2-hydroxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1235. 4-*tert*-Butyl-*N*-{1-[4-(2-methoxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 25 1236. 4-*tert*-Butyl-*N*-{1-[4-(2-hydroxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 30 1237. 4-*tert*-Butyl-*N*-{1-[4-(2-methoxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1238. 4-*tert*-Butyl-*N*-{1-[4-(2-hydroxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 35 1239. 4-*tert*-Butyl-*N*-{1-[4-(2-methoxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 40 1240. 4-*tert*-Butyl-*N*-{1-[4-(2-hydroxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1241. 4-*tert*-Butyl-*N*-{1-[4-(2-methoxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 45 1242. 4-*tert*-Butyl-*N*-{1-[4-(2-hydroxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

-200-

1243. 4-*tert*-Butyl-*N*-{1-[4-(2-methoxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 5 1244. *N*-[1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-dimethylaminobenzamide;
1245. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 1246. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1247. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 1248. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1249. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 1250. *N*-[1-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-dimethylamino-benzamide;
1251. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1252. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 1253. 4-Dimethylamino-*N*-[3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-benzamide;
1254. 4-[2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide;
- 35 1255. 4-[2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl-amide;
1256. 4-[2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenyl ester;
- 40 1257. 4-[2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl ester;
- 45 1258. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;

-201-

1259. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(piperidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 5 1260. 4-Dimethylamino-*N*-{3-methyl-1-[4-(morpholine-4-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1261. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(piperazine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 1262. 4-Dimethylamino-*N*-{3-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1263. 4-Dimethylamino-*N*-(3-methyl-1-{4-[2-(4-methyl-piperazin-1-yl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-butyl)-benzamide;
- 15 1264. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(2-piperazin-1-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1265. 4-Dimethylamino-*N*-{1-[4-(furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 20 1266. 4-Dimethylamino-*N*-{1-[4-(5-chloro-furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1267. 4-Dimethylamino-*N*-{1-[4-(thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 25 1268. 4-Dimethylamino-*N*-{1-[4-(5-chloro-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 30 1269. 4-Dimethylamino-*N*-{1-[4-(furan-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1270. 4-Dimethylamino-*N*-{1-[4-(thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 35 1271. 4-Dimethylamino-*N*-[1-(4-cyclopentanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide;
1272. 4-Dimethylamino-*N*-[1-(4-cyclohexanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide;
- 40 1273. 4-Dimethylamino-*N*-{1-[4-(cyclopent-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 45 1274. 4-Dimethylamino-*N*-{1-[4-(2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

-202-

1275. 4-Dimethylamino-*N*-{1-[4-(2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 5 1276. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1277. *N*-{1-[4-(1-Acetyl-pyrrolidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 10 1278. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(piperidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1279. *N*-{1-[4-(1-Acetyl-piperidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 15 1280. 4-Dimethylamino-*N*-{3-methyl-1-[6-oxo-4-(tetrahydro-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1281. *N*-{1-[4-(1-Amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 20 1282. *N*-{1-[4-(1-Amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
1283. *N*-{1-[4-(1-Amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 25 1284. *N*-{1-[4-(1-Acetyl-amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 30 1285. *N*-{1-[4-(1-Acetyl-amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 35 1286. *N*-{1-[4-(1-Acetyl-amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 40 1287. 4-Dimethylamino-*N*-{1-[4-(1-hydroxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1288. 4-Dimethylamino-*N*-{1-[4-(1-hydroxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 45 1289. 4-Dimethylamino-*N*-{1-[4-(1-hydroxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

-203-

1290. 4-Dimethylamino-*N*-{1-[4-(1-methoxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 5 1291. 4-Dimethylamino-*N*-{1-[4-(1-methoxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1292. 4-Dimethylamino-*N*-{1-[4-(1-methoxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 10 1293. *N*-{1-[4-(2-Amino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
1294. *N*-{1-[4-(2-Amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 15 1295. *N*-{1-[4-(2-Acetylamino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 20 1296. *N*-{1-[4-(2-Acetylamino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
1297. *N*-{1-[4-(2-Acetylamino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 25 1298. *N*-{1-[4-(2-Acetylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 30 1299. *N*-(1-{4-[2-(Acetyl-methyl-amino)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-4-dimethylamino-benzamide;
1300. 4-Dimethylamino-*N*-{1-[4-(2-dimethylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 35 1301. *N*-{1-[4-(2-Amino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
1302. *N*-{1-[4-(2-Acetylamino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 40 1303. *N*-{1-[4-(2-amino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 45 1304. *N*-{1-[4-(2-Acetylamino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;

-204-

1305. *N*-{1-[4-(2-amino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 5 1306. *N*-{1-[4-(2-Acetylamino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 10 1307. *N*-{1-[4-(2-Amino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
1308. *N*-{1-[4-(2-Acetylamino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 15 1309. 4-Dimethylamino-*N*-[3-methyl-1-(6-oxo-4-pentanoyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-benzamide;
1310. 4-Dimethylamino-*N*-{3-methyl-1-[4-(3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 1311. 4-Dimethylamino-*N*-{3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1312. *N*-{1-[4-(2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 25 1313. *N*-{1-[4-(2-Acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 30 1314. *N*-{1-[4-(2-Amino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
1315. *N*-{1-[4-(2-Acetylamino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 35 1316. *N*-{1-[4-(2-Amino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 40 1317. *N*-{1-[4-(2-Acetylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 45 1318. *N*-{1-[4-(2-Amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;

-205-

1319. *N*-{1-[4-(2-Acetylamino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 5 1320. *N*-{1-[4-(2-hydroxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
1321. *N*-{1-[4-(2-methoxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide;
- 10 1322. 4-Dimethylamino-*N*-{1-[4-(2-hydroxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1323. 4-Dimethylamino-*N*-{1-[4-(2-methoxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 15 1324. 4-Dimethylamino-*N*-{1-[4-(2-hydroxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 20 1325. 4-Dimethylamino-*N*-{1-[4-(2-methoxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1326. 4-Dimethylamino-*N*-{1-[4-(2-hydroxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 25 1327. 4-Dimethylamino-*N*-{1-[4-(2-methoxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1328. 4-Dimethylamino-*N*-{1-[4-(2-hydroxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 30 1329. 4-Dimethylamino-*N*-{1-[4-(2-methoxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1330. 4-Dimethylamino-*N*-{1-[4-(2-hydroxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 35 1331. 4-Dimethylamino-*N*-{1-[4-(2-methoxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 40 1332. 4-Dimethylamino-*N*-{1-[4-(2-hydroxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1333. 4-Dimethylamino-*N*-{1-[4-(2-methoxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 45 1334. *N*-[1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-thiophen-2-yl-benzamide;

1335. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 5 1336. *N*-{3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
1337. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 10 1338. *N*-{3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
1339. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 15 1340. *N*-[1-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-thiophen-2-yl-benzamide;
- 20 1341. *N*-{3-methyl-1-[6-oxo-4-(pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
1342. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 25 1343. *N*-[3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-4-thiophen-2-yl-benzamide;
1344. 4-[4-Methyl-2-(4-thiophen-2-yl-benzoylamino)-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide;
- 30 1345. 4-[4-Methyl-2-(4-thiophen-2-yl-benzoylamino)-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl-amide;
1346. 4-[4-Methyl-2-(4-thiophen-2-yl-benzoylamino)-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenyl ester;
- 35 1347. 4-[4-Methyl-2-(4-thiophen-2-yl-benzoylamino)-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl ester;
- 40 1348. *N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
1349. *N*-{3-methyl-1-[6-oxo-4-(piperidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 45 1350. *N*-{3-methyl-1-[4-(morpholine-4-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;

-207-

1351. *N*-{3-methyl-1-[6-oxo-4-(piperazine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 5 1352. *N*-{3-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
1353. *N*-(3-methyl-1-{4-[2-(4-methyl-piperazin-1-yl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-butyl)-4-thiophen-2-yl-benzamide;
- 10 1354. *N*-{3-methyl-1-[6-oxo-4-(2-piperazin-1-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
1355. *N*-{1-[4-(furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 15 1356. *N*-{1-[4-(5-chloro-furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 20 1357. *N*-{1-[4-(thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1358. *N*-{1-[4-(5-chloro-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 25 1359. *N*-{1-[4-(furan-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1360. *N*-{1-[4-(thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 30 1361. *N*-[1-(4-cyclopentanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-thiophen-2-yl-benzamide;
- 35 1362. *N*-[1-(4-cyclohexanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-thiophen-2-yl-benzamide;
1363. *N*-{1-[4-(cyclopent-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 40 1364. *N*-{1-[4-(2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1365. *N*-{1-[4-(2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 45 1366. *N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;

-208-

1367. *N*-{1-[4-(1-Acetyl-pyrrolidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 5 1368. *N*-{3-methyl-1-[6-oxo-4-(piperidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
1369. *N*-{1-[4-(1-Acetyl-piperidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 10 1370. *N*-{3-methyl-1-[6-oxo-4-(tetrahydro-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
1371. *N*-{1-[4-(1-Amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 15 1372. *N*-{1-[4-(1-Amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 20 1373. *N*-{1-[4-(1-Amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1374. *N*-{1-[4-(1-Acetylamino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 25 1375. *N*-{1-[4-(1-Acetylamino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 30 1376. *N*-{1-[4-(1-Acetylamino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 35 1377. *N*-{1-[4-(1-hydroxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1378. *N*-{1-[4-(1-hydroxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 40 1379. *N*-{1-[4-(1-hydroxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1380. *N*-{1-[4-(1-methoxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 45 1381. *N*-{1-[4-(1-methoxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;

1382. *N*-{1-[4-(1-methoxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 5 1383. *N*-{1-[4-(2-Amino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1384. *N*-{1-[4-(2-Amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 10 1385. *N*-{1-[4-(2-Acetyl-amino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1386. *N*-{1-[4-(2-Acetyl-amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 15 1387. *N*-{1-[4-(2-Acetyl-amino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 20 1388. *N*-{1-[4-(2-Acetyl-amino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1389. *N*-(1-{4-[2-(Acetyl-methyl-amino)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-4-thiophen-2-yl-benzamide;
- 25 1390. *N*-{1-[4-(2-dimethyl-amino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 30 1391. *N*-{1-[4-(2-Amino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1392. *N*-{1-[4-(2-Acetyl-amino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 35 1393. *N*-{1-[4-(2-amino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 40 1394. *N*-{1-[4-(2-Acetyl-amino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1395. *N*-{1-[4-(2-amino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 45 1396. *N*-{1-[4-(2-Acetyl-amino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;

1397. *N*-{1-[4-(2-Amino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 5 1398. *N*-{1-[4-(2-Acetylamino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 10 1399. *N*-[3-methyl-1-(6-oxo-4-pentanoyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-4-thiophen-2-yl-benzamide;
1400. *N*-{3-methyl-1-[4-(3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
- 15 1401. *N*-{3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-thiophen-2-yl-benzamide;
1402. *N*-{1-[4-(2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 20 1403. *N*-{1-[4-(2-Acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 25 1404. *N*-{1-[4-(2-Amino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1405. *N*-{1-[4-(2-Acetylamino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 30 1406. *N*-{1-[4-(2-Amino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 35 1407. *N*-{1-[4-(2-Acetylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1408. *N*-{1-[4-(2-Amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 40 1409. *N*-{1-[4-(2-Acetylamino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 45 1410. *N*-{1-[4-(2-hydroxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;

-211-

1411. *N*-{1-[4-(2-methoxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 5 1412. *N*-{1-[4-(2-hydroxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 10 1413. *N*-{1-[4-(2-methoxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1414. *N*-{1-[4-(2-hydroxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1415. *N*-{1-[4-(2-methoxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 15 1416. *N*-{1-[4-(2-hydroxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1417. *N*-{1-[4-(2-methoxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 20 1418. *N*-{1-[4-(2-hydroxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 25 1419. *N*-{1-[4-(2-methoxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 30 1420. *N*-{1-[4-(2-hydroxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1421. *N*-{1-[4-(2-methoxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 35 1422. *N*-{1-[4-(2-hydroxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
1423. *N*-{1-[4-(2-methoxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-thiophen-2-yl-benzamide;
- 40 1424. 5-Phenyl-thiophene-2-carboxylic acid-[1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide;
- 45 1425. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;

-212-

1426. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 5 1427. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 10 1428. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1429. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 1430. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 1431. 5-Phenyl-thiophene-2-carboxylic acid-[1-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide;
1432. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 1433. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 30 1434. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1435. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 1436. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 40 1437. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1438. 5-Phenyl-thiophene-2-carboxylic acid-[3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-amide;
- 45 1439. 4-{4-Methyl-2-[(5-phenyl-thiophene-2-carbonyl)-amino]-pentanoyl}-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide;

-213-

1440. 4-{4-Methyl-2-[(5-phenyl-thiophene-2-carbonyl)-amino]-pentanoyl}-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl-amide;
- 5 1441. 4-{4-Methyl-2-[(5-phenyl-thiophene-2-carbonyl)-amino]-pentanoyl}-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenyl ester;
1442. 4-{4-Methyl-2-[(5-phenyl-thiophene-2-carbonyl)-amino]-pentanoyl}-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl ester;
- 10 1443. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(pyrrolidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1444. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(piperidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 15 1445. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[4-(morpholine-4-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1446. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(piperazine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 1447. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 25 1448. 5-Phenyl-thiophene-2-carboxylic acid-(3-methyl-1-{4-[2-(4-methyl-piperazin-1-yl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-butyl)-amide;
- 30 1449. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(2-piperazin-1-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1450. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 35 1451. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(5-chloro-furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1452. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 40 1453. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(5-chloro-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 45 1454. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(furan-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;

1455. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 5 1456. 5-Phenyl-thiophene-2-carboxylic acid-[1-(4-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1457. 5-Phenyl-thiophene-2-carboxylic acid-[1-(4-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 10 1458. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(cyclopent-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1459. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 15 1460. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1461. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 20 1462. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-Acetyl-pyrrolidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 25 1463. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(piperidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
1464. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-Acetyl-piperidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 30 1465. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[6-oxo-4-(tetrahydrofuran-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
- 35 1466. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-Amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 40 1467. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-Amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 45 1468. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-Amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;

-215-

1469. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-Acetylamino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 5 1470. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-Acetylamino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 10 1471. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-Acetylamino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 15 1472. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-hydroxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 20 1473. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-hydroxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 25 1474. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-hydroxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 30 1475. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-methoxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 35 1476. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-methoxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 40 1477. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(1-methoxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 45 1478. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Amino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1479. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1480. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Acetylamino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;

-216-

1481. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Acetylamino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 5 1482. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Acetylamino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1483. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Acetylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 10 1484. 5-Phenyl-thiophene-2-carboxylic acid-(1-{4-[2-(Acetyl-methyl-amino)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-amide;
- 15 1485. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-dimethylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1486. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Amino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 20 1487. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Acetylamino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1488. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-amino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 25 1489. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Acetylamino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 30 1490. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-amino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 35 1491. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Acetylamino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 40 1492. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Amino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1493. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Acetylamino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 45 1494. 5-Phenyl-thiophene-2-carboxylic acid-[3-methyl-1-(6-oxo-4-pentanoyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-amide;

1495. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[4-(3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
5
1496. 5-Phenyl-thiophene-2-carboxylic acid-{3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide;
10
1497. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
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1498. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
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1499. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Amino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
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1500. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Acetylamino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
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1501. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Amino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
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1502. 5-Phenyl-thiophene-2-carboxylic acid {1-[4-(2-Acetylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
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1503. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
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1504. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-Acetylamino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1505. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-hydroxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1506. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-methoxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;

-218-

1507. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-hydroxy-3,3-dimethyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 5 1508. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-methoxy-3,3-dimethyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 10 1509. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-hydroxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 15 1510. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-methoxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 20 1511. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-hydroxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 25 1512. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-methoxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 30 1513. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-hydroxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 35 1514. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-methoxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 40 1515. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-hydroxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
- 45 1516. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-methoxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1517. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-hydroxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1518. 5-Phenyl-thiophene-2-carboxylic acid-{1-[4-(2-methoxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-amide;
1519. *N*-[1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-pyrrolidin-1-ylbenzamide;

-219-

1520. *N*-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 5 1521. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
1522. *N*-{3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 10 1523. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
1524. *N*-{3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 15 1525. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 20 1526. *N*-[1-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-pyrrolidin-1-yl-benzamide;
1527. *N*-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 25 1528. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
1529. *N*-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 30 1530. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 35 1531. *N*-{3-methyl-1-[6-oxo-4-(pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
1532. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 40 1533. *N*-[3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-4-pyrrolidin-1-yl-benzamide;
1534. 4-[2-(4-pyrrolidin-1-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide;
- 45 1535. 4-[2-(4-pyrrolidin-1-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl-amide;

1536. 4-[2-(4-pyrrolidin-1-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenyl ester;
- 5 1537. 4-[2-(4-pyrrolidin-1-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl ester;
1538. *N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 10 1539. *N*-{3-methyl-1-[6-oxo-4-(piperidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 15 1540. *N*-{3-methyl-1-[4-(morpholine-4-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
1541. *N*-{3-methyl-1-[6-oxo-4-(piperazine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 20 1542. *N*-{3-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
1543. *N*-(3-methyl-1-[4-[2-(4-methyl-piperazin-1-yl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl)-4-pyrrolidin-1-yl-benzamide;
- 25 1544. *N*-{3-methyl-1-[6-oxo-4-(2-piperazin-1-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
1545. *N*-{1-[4-(furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 30 1546. *N*-{1-[4-(5-chloro-furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1547. *N*-{1-[4-(thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 35 1548. *N*-{1-[4-(5-chloro-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 40 1549. *N*-{1-[4-(furan-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1550. *N*-{1-[4-(thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 45 1551. *N*-[1-(4-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;

1552. *N*-[1-(4-cyclohexanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-pyrrolidin-1-yl-benzamide;
- 5 1553. *N*-{1-[4-(cyclopent-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1554. *N*-{1-[4-(2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 10 1555. *N*-{1-[4-(2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1556. 4-Pyrrolidin-1-yl-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 1557. *N*-{1-[4-(1-Acetyl-pyrrolidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 20 1558. *N*-{3-methyl-1-[6-oxo-4-(piperidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
1559. *N*-{1-[4-(1-Acetyl-piperidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 25 1560. *N*-{3-methyl-1-[6-oxo-4-(tetrahydro-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
1561. *N*-{1-[4-(1-Amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 30 1562. *N*-{1-[4-(1-Amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1563. *N*-{1-[4-(1-Amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 35 1564. *N*-{1-[4-(1-Acetylamino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 40 1565. *N*-{1-[4-(1-Acetylamino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 45 1566. *N*-{1-[4-(1-Acetylamino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;

-222-

1567. *N*-{1-[4-(1-hydroxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 5 1568. *N*-{1-[4-(1-hydroxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1569. *N*-{1-[4-(1-hydroxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 10 1570. *N*-{1-[4-(1-methoxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1571. *N*-{1-[4-(1-methoxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 15 1572. *N*-{1-[4-(1-methoxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 20 1573. *N*-{1-[4-(2-Amino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1574. *N*-{1-[4-(2-Amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 25 1575. *N*-{1-[4-(2-Acetylamino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 30 1576. *N*-{1-[4-(2-Acetylamino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 35 1577. *N*-{1-[4-(2-Acetylamino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1578. *N*-{1-[4-(2-Acetylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 40 1579. *N*-(1-{4-[2-(Acetyl-methyl-amino)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-4-pyrrolidin-1-yl-benzamide;
1580. *N*-{1-[4-(2-dimethylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 45 1581. *N*-{1-[4-(2-Amino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;

-223-

1582. *N*-{1-[4-(2-Acetylamino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 5 1583. *N*-{1-[4-(2-amino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1584. *N*-{1-[4-(2-Acetylamino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 10 1585. *N*-{1-[4-(2-amino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1586. *N*-{1-[4-(2-Acetylamino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 15 1587. *N*-{1-[4-(2-Amino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 20 1588. *N*-{1-[4-(2-Acetylamino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1589. *N*-[3-methyl-1-(6-oxo-4-pentanoyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-4-pyrrolidin-1-yl-benzamide;
- 25 1590. *N*-{3-methyl-1-[4-(3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
- 30 1591. *N*-{3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-pyrrolidin-1-yl-benzamide;
1592. *N*-{1-[4-(2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 35 1593. *N*-{1-[4-(2-Acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 40 1594. *N*-{1-[4-(2-Amino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1595. *N*-{1-[4-(2-Acetylamino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 45 1596. *N*-{1-[4-(2-Amino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;

1597. *N*-{1-[4-(2-Acetylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 5 1598. *N*-{1-[4-(2-Amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 10 1599. *N*-{1-[4-(2-Acetylamino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1600. *N*-{1-[4-(2-hydroxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 15 1601. *N*-{1-[4-(2-methoxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 20 1602. *N*-{1-[4-(2-hydroxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1603. *N*-{1-[4-(2-methoxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 25 1604. *N*-{1-[4-(2-hydroxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1605. *N*-{1-[4-(2-methoxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 30 1606. *N*-{1-[4-(2-hydroxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1607. *N*-{1-[4-(2-methoxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 35 1608. *N*-{1-[4-(2-hydroxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 40 1609. *N*-{1-[4-(2-methoxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 45 1610. *N*-{1-[4-(2-hydroxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1611. *N*-{1-[4-(2-methoxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;

1612. *N*-{1-[4-(2-hydroxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
- 5 1613. *N*-{1-[4-(2-methoxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-pyrrolidin-1-yl-benzamide;
1614. *N*-[1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-morpholin-4-ylbenzamide;
- 10 1615. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
1616. *N*-{3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 15 1617. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 20 1618. *N*-{3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
1619. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 25 1620. *N*-[1-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-morpholin-4-yl-benzamide;
1621. *N*-{3-methyl-1-[6-oxo-4-(pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 30 1622. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 35 1623. *N*-[3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-4-morpholin-4-yl-benzamide;
1624. 4-[2-(4-morpholin-4-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide;
- 40 1625. 4-[2-(4-morpholin-4-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl-amide;
1626. 4-[2-(4-morpholin-4-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenyl ester;
- 45 1627. 4-[2-(4-morpholin-4-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl ester;

1628. *N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 5 1629. *N*-{3-methyl-1-[6-oxo-4-(piperidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
1630. *N*-{3-methyl-1-[4-(morpholine-4-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 10 1631. *N*-{3-methyl-1-[6-oxo-4-(piperazine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
1632. *N*-{3-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 15 1633. *N*-(3-methyl-1-{4-[2-(4-methyl-piperazin-1-yl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-butyl)-4-morpholin-4-yl-benzamide;
- 20 1634. *N*-{3-methyl-1-[6-oxo-4-(2-piperazin-1-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
1635. *N*-{1-[4-(furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 25 1636. *N*-{1-[4-(5-chloro-furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1637. *N*-{1-[4-(thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 30 1638. *N*-{1-[4-(5-chloro-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 35 1639. *N*-{1-[4-(furan-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1640. *N*-{1-[4-(thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 40 1641. *N*-[1-(4-cyclopentanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-morpholin-4-yl-benzamide;
1642. *N*-[1-(4-cyclohexanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-morpholin-4-yl-benzamide;
- 45 1643. *N*-{1-[4-(cyclopent-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;

-227-

1644. *N*-{1-[4-(2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 5 1645. *N*-{1-[4-(2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1646. 4-morpholin-4-yl-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 1647. *N*-{1-[4-(1-Acetyl-pyrrolidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 15 1648. *N*-{3-methyl-1-[6-oxo-4(piperidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
1649. *N*-{1-[4-(1-Acetyl-piperidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 20 1650. *N*-{3-methyl-1-[6-oxo-4-(tetrahydro-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
1651. *N*-{1-[4-(1-Amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 25 1652. *N*-{1-[4-(1-Amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1653. *N*-{1-[4-(1-Amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 30 1654. *N*-{1-[4-(1-Acetylamino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 35 1655. *N*-{1-[4-(1-Acetylamino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 40 1656. *N*-{1-[4-(1-Acetylamino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 45 1657. *N*-{1-[4-(1-hydroxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1658. *N*-{1-[4-(1-hydroxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;

1659. *N*-{1-[4-(1-hydroxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 5 1660. *N*-{1-[4-(1-methoxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1661. *N*-{1-[4-(1-methoxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 10 1662. *N*-{1-[4-(1-methoxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1663. *N*-{1-[4-(2-Amino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 15 1664. *N*-{1-[4-(2-Amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 20 1665. *N*-{1-[4-(2-Acetylamino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 25 1666. *N*-{1-[4-(2-Acetylamino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1667. *N*-{1-[4-(2-Acetylamino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 30 1668. *N*-{1-[4-(2-Acetylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1669. *N*-(1-{4-[2-(Acetyl-methyl-amino)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-4-morpholin-4-yl-benzamide;
- 35 1670. *N*-{1-[4-(2-dimethylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 40 1671. *N*-{1-[4-(2-Amino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1672. *N*-{1-[4-(2-Acetylamino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 45 1673. *N*-{1-[4-(2-amino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;

-229-

1674. *N*-{1-[4-(2-Acetylamino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 5 1675. *N*-{1-[4-(2-amino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 10 1676. *N*-{1-[4-(2-Acetylamino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1677. *N*-{1-[4-(2-Amino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 15 1678. *N*-{1-[4-(2-Acetylamino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 20 1679. *N*-[3-methyl-1-(6-oxo-4-pentanoyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-4-morpholin-4-yl-benzamide;
1680. *N*-{3-methyl-1-[4-(3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
- 25 1681. *N*-{3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-morpholin-4-yl-benzamide;
1682. *N*-{1-[4-(2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 30 1683. *N*-{1-[4-(2-Acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 35 1684. *N*-{1-[4-(2-Amino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1685. *N*-{1-[4-(2-Acetylamino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 40 1686. *N*-{1-[4-(2-Amino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 45 1687. *N*-{1-[4-(2-Acetylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1688. *N*-{1-[4-(2-Amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;

1689. *N*-{1-[4-(2-Acetylamino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 5
1690. *N*-{1-[4-(2-hydroxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1691. *N*-{1-[4-(2-methoxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 10
1692. *N*-{1-[4-(2-hydroxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1693. *N*-{1-[4-(2-methoxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 15
1694. *N*-{1-[4-(2-hydroxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 20
1695. *N*-{1-[4-(2-methoxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1696. *N*-{1-[4-(2-hydroxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 25
1697. *N*-{1-[4-(2-methoxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 30
1698. *N*-{1-[4-(2-hydroxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 35
1699. *N*-{1-[4-(2-methoxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1700. *N*-{1-[4-(2-hydroxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 40
1701. *N*-{1-[4-(2-methoxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
1702. *N*-{1-[4-(2-hydroxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;
- 45
1703. *N*-{1-[4-(2-methoxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-morpholin-4-yl-benzamide;

1704. *N*-[1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-piperazin-1-ylbenzamide;
- 5 1705. *N*-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
1706. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 10 1707. *N*-{3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
1708. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 15 1709. *N*-{3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 20 1710. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
1711. *N*-[1-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-piperazin-1-yl-benzamide;
- 25 1712. *N*-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
1713. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 30 1714. *N*-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
1715. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 35 1716. *N*-{3-methyl-1-[6-oxo-4-(pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 40 1717. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
1718. *N*-[3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-4-piperazin-1-yl-benzamide;
- 45 1719. 4-[2-(4-piperazin-1-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide;

1720. 4-[2-(4-piperazin-1-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl-amide;
- 5 1721. 4-[2-(4-piperazin-1-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenyl ester;
1722. 4-[2-(4-piperazin-1-yl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl ester;
- 10 1723. *N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
1724. *N*-{3-methyl-1-[6-oxo-4-(piperidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 15 1725. *N*-{3-methyl-1-[4-(morpholine-4-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 20 1726. *N*-{3-methyl-1-[6-oxo-4-(piperazine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
1727. *N*-{3-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 25 1728. *N*-(3-methyl-1-{4-[2-(4-methyl-piperazin-1-yl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-butyl)-4-piperazin-1-yl-benzamide;
1729. *N*-{3-methyl-1-[6-oxo-4-(2-piperazin-1-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 30 1730. *N*-{1-[4-(furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 35 1731. *N*-{1-[4-(5-chloro-furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1732. *N*-{1-[4-(thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 40 1733. *N*-{1-[4-(5-chloro-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1734. *N*-{1-[4-(furan-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 45 1735. *N*-{1-[4-(thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;

-233-

1736. *N*-[1-(4-cyclopentanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-piperazin-1-yl-benzamide;
- 5 1737. *N*-[1-(4-cyclohexanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-piperazin-1-yl-benzamide;
1738. *N*-{1-[4-(cyclopent-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 10 1739. *N*-{1-[4-(2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1740. *N*-{1-[4-(2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 15 1741. 4-piperazin-1-yl-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 1742. *N*-{1-[4-(1-Acetyl-pyrrolidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1743. *N*-{3-methyl-1-[6-oxo-4-(piperidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 25 1744. *N*-{1-[4-(1-Acetyl-piperidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1745. *N*-{3-methyl-1-[6-oxo-4-(tetrahydro-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 30 1746. *N*-{1-[4-(1-Amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 35 1747. *N*-{1-[4-(1-Amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1748. *N*-{1-[4-(1-Amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 40 1749. *N*-{1-[4-(1-Acetylamino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 45 1750. *N*-{1-[4-(1-Acetylamino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;

-234-

1751. *N*-{1-[4-(1-Acetylamino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 5 1752. *N*-{1-[4-(1-hydroxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1753. *N*-{1-[4-(1-hydroxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 10 1754. *N*-{1-[4-(1-hydroxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1755. *N*-{1-[4-(1-methoxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 15 1756. *N*-{1-[4-(1-methoxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 20 1757. *N*-{1-[4-(1-methoxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1758. *N*-{1-[4-(2-Amino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 25 1759. *N*-{1-[4-(2-Amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 30 1760. *N*-{1-[4-(2-Acetylamino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 35 1761. *N*-{1-[4-(2-Acetylamino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1762. *N*-{1-[4-(2-Acetylamino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 40 1763. *N*-{1-[4-(2-Acetylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1764. *N*-(1-{4-[2-(Acetyl-methyl-amino)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-4-piperazin-1-yl-benzamide;
- 45 1765. *N*-{1-[4-(2-dimethylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;

-235-

1766. *N*-{1-[4-(2-Amino-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 5 1767. *N*-{1-[4-(2-Acetylamino-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1768. *N*-{1-[4-(2-amino-3-methyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 10 1769. *N*-{1-[4-(2-Acetylamino-3-methyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1770. *N*-{1-[4-(2-amino-3,3-dimethyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 15 1771. *N*-{1-[4-(2-Acetylamino-3,3-dimethyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 20 1772. *N*-{1-[4-(2-Amino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1773. *N*-{1-[4-(2-Acetylamino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 25 1774. *N*-[3-methyl-1-(6-oxo-4-pentanoyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-4-piperazin-1-yl-benzamide;
- 30 1775. *N*-{3-methyl-1-[4-(3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
1776. *N*-{3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-piperazin-1-yl-benzamide;
- 35 1777. *N*-{1-[4-(2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 40 1778. *N*-{1-[4-(2-Acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 45 1779. *N*-{1-[4-(2-Amino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1780. *N*-{1-[4-(2-Acetylamino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;

-236-

1781. *N*-{1-[4-(2-Amino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 5 1782. *N*-{1-[4-(2-Acetylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1783. *N*-{1-[4-(2-Amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 10 1784. *N*-{1-[4-(2-Acetylamino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 15 1785. *N*-{1-[4-(2-hydroxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1786. *N*-{1-[4-(2-methoxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 20 1787. *N*-{1-[4-(2-hydroxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1788. *N*-{1-[4-(2-methoxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 25 1789. *N*-{1-[4-(2-hydroxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 30 1790. *N*-{1-[4-(2-methoxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1791. *N*-{1-[4-(2-hydroxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 35 1792. *N*-{1-[4-(2-methoxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1793. *N*-{1-[4-(2-hydroxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 40 1794. *N*-{1-[4-(2-methoxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 45 1795. *N*-{1-[4-(2-hydroxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;

-237-

1796. *N*-{1-[4-(2-methoxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 5 1797. *N*-{1-[4-(2-hydroxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
1798. *N*-{1-[4-(2-methoxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-piperazin-1-yl-benzamide;
- 10 1799. *N*-[1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-(4-methyl-piperazin-1-yl)benzamide;
1800. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 15 1801. *N*-{3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 20 1802. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 25 1803. *N*-{3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 30 1804. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1805. *N*-[1-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-(4-methyl-piperazin-1-yl)-benzamide;
- 35 1806. *N*-{3-methyl-1-[6-oxo-4-(pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 40 1807. *N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1808. *N*-[3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-4-(4-methyl-piperazin-1-yl)-benzamide;
- 45 1809. 4-[2-(4-(4-methyl-piperazin-1-yl)-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide;

-238-

1810. 4-[2-(4-(4-methyl-piperazin-1-yl)-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl-amide;
- 5 1811. 4-[2-(4-(4-methyl-piperazin-1-yl)-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenyl ester;
1812. 4-[2-(4-(4-methyl-piperazin-1-yl)-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl ester;
- 10 1813. *N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1814. *N*-{3-methyl-1-[6-oxo-4-(piperidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 15 1815. *N*-{3-methyl-1-[4-(morpholine-4-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1816. *N*-{3-methyl-1-[6-oxo-4-(piperazine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 20 1817. *N*-{3-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 25 1818. *N*-(3-methyl-1-{4-[2-(4-methyl-piperazin-1-yl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-butyl)-4-(4-methyl-piperazin-1-yl)-benzamide;
- 30 1819. *N*-{3-methyl-1-[6-oxo-4-(2-piperazin-1-yl)-acetyl]-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1820. *N*-{1-[4-(furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 35 1821. *N*-{1-[4-(5-chloro-furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 40 1822. *N*-{1-[4-(thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1823. *N*-{1-[4-(5-chloro-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 45 1824. *N*-{1-[4-(furan-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;

1825. *N*-{1-[4-(thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 5 1826. *N*-[1-(4-cyclopentanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-(4-methyl-piperazin-1-yl)-benzamide;
1827. *N*-[1-(4-cyclohexanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-(4-methyl-piperazin-1-yl)-benzamide;
- 10 1828. *N*-{1-[4-(cyclopent-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 15 1829. *N*-{1-[4-(2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1830. *N*-{1-[4-(2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 20 1831. 4-(4-methyl-piperazin-1-yl)-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1832. *N*-{1-[4-(1-Acetyl-pyrrolidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 25 1833. *N*-{3-methyl-1-[6-oxo-4-(piperidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 30 1834. *N*-{1-[4-(1-Acetyl-piperidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 35 1835. *N*-{3-methyl-1-[6-oxo-4-(tetrahydro-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 40 1836. *N*-{1-[4-(1-Amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 45 1837. *N*-{1-[4-(1-Amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;

-240-

1838. *N*-{1-[4-(1-Amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 5 1839. *N*-{1-[4-(1-Acetylamino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 10 1840. *N*-{1-[4-(1-Acetylamino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 15 1841. *N*-{1-[4-(1-Acetylamino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 20 1842. *N*-{1-[4-(1-hydroxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 25 1843. *N*-{1-[4-(1-hydroxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 30 1844. *N*-{1-[4-(1-hydroxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 35 1845. *N*-{1-[4-(1-methoxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 40 1846. *N*-{1-[4-(1-methoxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 45 1847. *N*-{1-[4-(1-methoxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1848. *N*-{1-[4-(2-Amino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1849. *N*-{1-[4-(2-Amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;

-241-

1850. *N*-{1-[4-(2-Acetylamino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 5 1851. *N*-{1-[4-(2-Acetylamino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 10 1852. *N*-{1-[4-(2-Acetylamino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 15 1853. *N*-{1-[4-(2-Acetylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1854. *N*-(1-{4-[2-(Acetyl-methyl-amino)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-4-(4-methyl-piperazin-1-yl)-benzamide;
- 20 1855. *N*-{1-[4-(2-dimethylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 25 1856. *N*-{1-[4-(2-Amino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1857. *N*-{1-[4-(2-Acetylamino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 30 1858. *N*-{1-[4-(2-amino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 35 1859. *N*-{1-[4-(2-Acetylamino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 40 1860. *N*-{1-[4-(2-amino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 45 1861. *N*-{1-[4-(2-Acetylamino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1862. *N*-{1-[4-(2-Amino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;

-242-

1863. *N*-{1-[4-(2-Acetylamino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1864. *N*-[3-methyl-1-(6-oxo-4-pentanoyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-4-(4-methyl-piperazin-1-yl)-benzamide;
1865. *N*-{3-methyl-1-[4-(3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1866. *N*-{3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1867. *N*-{1-[4-(2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1868. *N*-{1-[4-(2-Acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1869. *N*-{1-[4-(2-Amino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1870. *N*-{1-[4-(2-Acetylamino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1871. *N*-{1-[4-(2-Amino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1872. *N*-{1-[4-(2-Acetylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1873. *N*-{1-[4-(2-Amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1874. *N*-{1-[4-(2-Acetylamino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1875. *N*-{1-[4-(2-hydroxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;

1876. *N*-{1-[4-(2-methoxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1877. *N*-{1-[4-(2-hydroxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1878. *N*-{1-[4-(2-methoxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1879. *N*-{1-[4-(2-hydroxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1880. *N*-{1-[4-(2-methoxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1881. *N*-{1-[4-(2-hydroxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1882. *N*-{1-[4-(2-methoxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1883. *N*-{1-[4-(2-hydroxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1884. *N*-{1-[4-(2-methoxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1885. *N*-{1-[4-(2-hydroxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1886. *N*-{1-[4-(2-methoxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
1887. *N*-{1-[4-(2-hydroxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;

-244-

1888. *N*-{1-[4-(2-methoxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-(4-methyl-piperazin-1-yl)-benzamide;
- 5 1889. *N*-[1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-aminobenzamide;
1890. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 1891. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1892. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 1893. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 1894. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1895. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 1896. *N*-[1-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-amino-benzamide;
1897. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 1898. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 1899. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1900. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 40 1901. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1902. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 45 1903. 4-Amino-*N*-[3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-benzamide;

-245-

1904. 4-[2-(4-amino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide;
- 5 1905. 4-[2-(4-amino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl-amide;
1906. 4-[2-(4-amino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenyl ester;
- 10 1907. 4-[2-(4-amino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl ester;
1908. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 1909. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(piperidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 1910. 4-Amino-*N*-{3-methyl-1-[4-(morpholine-4-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1911. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(piperazine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 1912. 4-Amino-*N*-{3-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1913. 4-Amino-*N*-(3-methyl-1-{4-[2-(4-methyl-piperazin-1-yl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-butyl)-benzamide;
- 30 1914. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(2-piperazin-1-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1915. 4-Amino-*N*-{1-[4-(furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 35 1916. 4-Amino-*N*-{1-[4-(5-chloro-furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 40 1917. 4-Amino-*N*-{1-[4-(thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1918. 4-Amino-*N*-{1-[4-(5-chloro-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 45 1919. 4-Amino-*N*-{1-[4-(furan-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

1920. 4-Amino-*N*-{1-[4-(thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 5 1921. 4-Amino-*N*-[1-(4-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1922. 4-Amino-*N*-[1-(4-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 10 1923. 4-Amino-*N*-{1-[4-(cyclopent-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1924. 4-Amino-*N*-{1-[4-(2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 15 1925. 4-Amino-*N*-{1-[4-(2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 20 1926. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1927. *N*-{1-[4-(1-Acetyl-pyrrolidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 25 1928. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(piperidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1929. *N*-{1-[4-(1-Acetyl-piperidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 30 1930. 4-Amino-*N*-{3-methyl-1-[6-oxo-4-(tetrahydro-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 1931. *N*-{1-[4-(1-Amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-Amino-benzamide;
1932. *N*-{1-[4-(1-Amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 40 1933. *N*-{1-[4-(1-Amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 45 1934. *N*-{1-[4-(1-Acetylamino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
1935. *N*-{1-[4-(1-Acetylamino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;

1936. *N*-{1-[4-(1-Acetylamino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 5 1937. 4-Amino-*N*-{1-[4-(1-hydroxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1938. 4-Amino-*N*-{1-[4-(1-hydroxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 10 1939. 4-Amino-*N*-{1-[4-(1-hydroxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1940. 4-Amino-*N*-{1-[4-(1-methoxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 15 1941. 4-Amino-*N*-{1-[4-(1-methoxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 20 1942. 4-Amino-*N*-{1-[4-(1-methoxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1943. *N*-{1-[4-(2-amino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 25 1944. *N*-{1-[4-(2-amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
1945. *N*-{1-[4-(2-acetylamino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 30 1946. *N*-{1-[4-(2-acetylamino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 35 1947. *N*-{1-[4-(2-acetylamino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
1948. *N*-{1-[4-(2-acetylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 40 1949. *N*-(1-{4-[2-(acetyl-methyl-amino)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-4-amino-benzamide;
- 45 1950. 4-Amino-*N*-{1-[4-(2-dimethylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1951. *N*-{1-[4-(2-amino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;

1952. *N*-{1-[4-(2-acetylamino-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 5 1953. *N*-{1-[4-(2-amino-3-methyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
1954. *N*-{1-[4-(2-acetylamino-3-methyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 10 1955. *N*-{1-[4-(2-amino-3,3-dimethyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
1956. *N*-{1-[4-(2-acetylamino-3,3-dimethyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 15 1957. *N*-{1-[4-(2-amino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 20 1958. *N*-{1-[4-(2-acetylamino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
1959. 4-Amino-*N*-[3-methyl-1-(6-oxo-4-pentanoyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-benzamide;
- 25 1960. 4-Amino-*N*-{3-methyl-1-[4-(3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1961. 4-Amino-*N*-{3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 1962. *N*-{1-[4-(2-amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 35 1963. *N*-{1-[4-(2-acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
1964. *N*-{1-[4-(2-amino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 40 1965. *N*-{1-[4-(2-acetylamino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
1966. *N*-{1-[4-(2-amino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 45 1967. *N*-{1-[4-(2-acetylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;

1968. *N*-{1-[4-(2-amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 5 1969. *N*-{1-[4-(2-acetyl-amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
1970. *N*-{1-[4-(2-hydroxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
- 10 1971. *N*-{1-[4-(2-methoxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-amino-benzamide;
1972. 4-Amino-*N*-{1-[4-(2-hydroxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 15 1973. 4-Amino-*N*-{1-[4-(2-methoxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 20 1974. 4-Amino-*N*-{1-[4-(2-hydroxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1975. 4-Amino-*N*-{1-[4-(2-methoxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 25 1976. 4-Amino-*N*-{1-[4-(2-hydroxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1977. 4-Amino-*N*-{1-[4-(2-methoxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 30 1978. 4-Amino-*N*-{1-[4-(2-hydroxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 35 1979. 4-Amino-*N*-{1-[4-(2-methoxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1980. 4-Amino-*N*-{1-[4-(2-hydroxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 40 1981. 4-Amino-*N*-{1-[4-(2-methoxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
1982. 4-Amino-*N*-{1-[4-(2-hydroxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 45 1983. 4-Amino-*N*-{1-[4-(2-methoxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

-250-

1984. *N*-[1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-diethylaminobenzamide;
- 5 1985. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1986. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 10 1987. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1988. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 1989. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 1990. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1991. *N*-[1-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-diethylamino-benzamide;
- 25 1992. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1993. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 1994. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1995. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 1996. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 40 1997. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-sulfonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
1998. 4-Diethylamino-*N*-[3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-benzamide;
- 45 1999. 4-[2-(4-diethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide;

-251-

2000. 4-[2-(4-diethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl-amide;
- 5 2001. 4-[2-(4-diethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenyl ester;
2002. 4-[2-(4-diethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid isobutyl ester;
- 10 2003. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
2004. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(piperidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 15 2005. 4-Diethylamino-*N*-{3-methyl-1-[4-(morpholine-4-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 2006. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(piperazine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
2007. 4-Diethylamino-*N*-{3-methyl-1-[4-(4-methyl-piperazine-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 2008. 4-Diethylamino-*N*-(3-methyl-1-{4-[2-(4-methyl-piperazin-1-yl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-butyl)-benzamide;
2009. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(2-piperazin-1-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 2010. 4-Diethylamino-*N*-{1-[4-(furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 35 2011. 4-Diethylamino-*N*-{1-[4-(5-chloro-furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
2012. 4-Diethylamino-*N*-{1-[4-(thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 40 2013. 4-Diethylamino-*N*-{1-[4-(5-chloro-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
2014. 4-Diethylamino-*N*-{1-[4-(furan-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 45 2015. 4-Diethylamino-*N*-{1-[4-(thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

-252-

2016. 4-Diethylamino-*N*-[1-(4-cyclopentanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide;
- 5 2017. 4-Diethylamino-*N*-[1-(4-cyclohexanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide;
2018. 4-Diethylamino-*N*-{1-[4-(cyclopent-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 10 2019. 4-Diethylamino-*N*-{1-[4-(2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
2020. 4-Diethylamino-*N*-{1-[4-(2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 15 2021. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 20 2022. *N*-{1-[4-(1-Acetyl-pyrrolidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
2023. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(piperidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 25 2024. *N*-{1-[4-(1-Acetyl-piperidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
2025. 4-Diethylamino-*N*-{3-methyl-1-[6-oxo-4-(tetrahydro-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 30 2026. *N*-{1-[4-(1-Amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 35 2027. *N*-{1-[4-(1-Amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
2028. *N*-{1-[4-(1-Amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 40 2029. *N*-{1-[4-(1-Acetyl-amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 45 2030. *N*-{1-[4-(1-Acetyl-amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;

-253-

2031. *N*-{1-[4-(1-Acetylamino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 5 2032. 4-Diethylamino-*N*-{1-[4-(1-hydroxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
2033. 4-Diethylamino-*N*-{1-[4-(1-hydroxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 10 2034. 4-Diethylamino-*N*-{1-[4-(1-hydroxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
2035. 4-Diethylamino-*N*-{1-[4-(1-methoxy-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 15 2036. 4-Diethylamino-*N*-{1-[4-(1-methoxy-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 20 2037. 4-Diethylamino-*N*-{1-[4-(1-methoxy-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
2038. *N*-{1-[4-(2-Amino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 25 2039. *N*-{1-[4-(2-Amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
2040. *N*-{1-[4-(2-Acetylamino-2-cyclopentyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 30 2041. *N*-{1-[4-(2-Acetylamino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 35 2042. *N*-{1-[4-(2-Acetylamino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 40 2043. *N*-{1-[4-(2-Acetylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
2044. *N*-(1-{4-[2-(Acetyl-methyl-amino)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-4-diethylamino-benzamide;
- 45 2045. 4-Diethylamino-*N*-{1-[4-(2-dimethylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

-254-

2046. *N*-{1-[4-(2-Amino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 5 2047. *N*-{1-[4-(2-Acetylamino-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
2048. *N*-{1-[4-(2-amino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 10 2049. *N*-{1-[4-(2-Acetylamino-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
2050. *N*-{1-[4-(2-amino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 15 2051. *N*-{1-[4-(2-Acetylamino-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 20 2052. *N*-{1-[4-(2-Amino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
2053. *N*-{1-[4-(2-Acetylamino-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 25 2054. 4-Diethylamino-*N*-[3-methyl-1-(6-oxo-4-pentanoyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-benzamide;
- 30 2055. 4-Diethylamino-*N*-{3-methyl-1-[4-(3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
2056. 4-Diethylamino-*N*-{3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide;
- 35 2057. *N*-{1-[4-(2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
2058. *N*-{1-[4-(2-Acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 40 2059. *N*-{1-[4-(2-Amino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 45 2060. *N*-{1-[4-(2-Acetylamino-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;

-255-

2061. *N*-{1-[4-(2-Amino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 5 2062. *N*-{1-[4-(2-Acetylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
2063. *N*-{1-[4-(2-Amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 10 2064. *N*-{1-[4-(2-Acetylamino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 15 2065. *N*-{1-[4-(2-hydroxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
2066. *N*-{1-[4-(2-methoxy-3-methyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-diethylamino-benzamide;
- 20 2067. 4-Diethylamino-*N*-{1-[4-(2-hydroxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
2068. 4-Diethylamino-*N*-{1-[4-(2-methoxy-3,3-dimethyl-butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 25 2069. 4-Diethylamino-*N*-{1-[4-(2-hydroxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 30 2070. 4-Diethylamino-*N*-{1-[4-(2-methoxy-3-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
2071. 4-Diethylamino-*N*-{1-[4-(2-hydroxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 35 2072. 4-Diethylamino-*N*-{1-[4-(2-methoxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
2073. 4-Diethylamino-*N*-{1-[4-(2-hydroxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 40 2074. 4-Diethylamino-*N*-{1-[4-(2-methoxy-4,4-dimethyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;
- 45 2075. 4-Diethylamino-*N*-{1-[4-(2-hydroxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

-256-

2076. 4-Diethylamino-*N*-{1-[4-(2-methoxy-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

2077. 4-Diethylamino-*N*-{1-[4-(2-hydroxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

2078. 4-Diethylamino-*N*-{1-[4-(2-methoxy-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide;

To those skilled in the practices of organic chemistry, compounds of general formula (I) may be readily synthesised by a number of chemical strategies, performed either in solution or on the solid phase (see Atherton, E. and Sheppard, R. C. In '*Solid Phase Peptide Synthesis: A Practical Approach*', Oxford University Press, Oxford, U.K. 1989, for a general review of solid phase synthesis principles). The solid phase strategy is attractive in being able to generate many thousands of analogues, typically on a 5-100mg scale, through established parallel synthesis methodologies (e.g. see (a) Bastos, M.; Maeji, N. J.; Abeles, R. H. *Proc. Natl. Acad. Sci. USA*, 92, 6738-6742, 1995).

Therefore, one strategy for the synthesis of compounds of general formula (I) comprises:-

(a) Preparation of an appropriately functionalised and protected bicyclic ketone building block in solution.

(b) Attachment of the building block (a) to the solid phase through a linker that is stable to the conditions of synthesis, but readily labile to cleavage at the end of a synthesis (see James, I. W., *Tetrahedron*, *55*(Report N^o 489), 4855-4946, 1999, for examples of the 'linker' function as applied to solid phase synthesis).

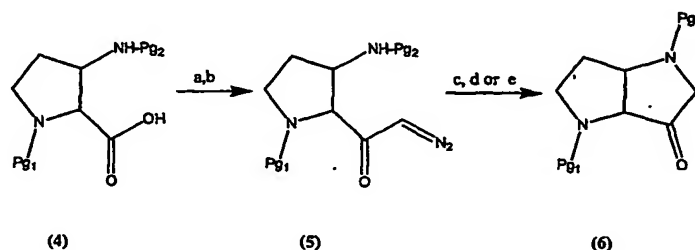
(c) Solid phase organic chemistry (see Brown, R. D. *J. Chem. Soc., Perkin Trans. I*, 19, 3293-3320, 1998), to construct the remainder of the molecule.

(d) Compound cleavage from the solid phase into solution.

(e) Cleavage work-up and compound analysis.

The first stage in a synthesis of compounds of general formula (I) is the preparation in solution of a functionalised and protected building block. Typical schemes towards the hexahydropyrrolo[3,2-*b*]pyrrol-3-one (6) are detailed in Schemes 1-3, a hexahydropyrrolo[3,2-*c*]pyrazol-6-one (21) in Scheme 4 and a hexahydro-2-oxa-1,4-diazapentalen-6-one (26) in Scheme 5. The synthetic descriptions detailed in Schemes 6-18 could equally be applied using each of the scaffolds of general formula (I).

10 'Pg₁' and 'Pg₂' denotes suitable amine protecting groups such as the 9-fluorenyl methoxycarbonyl (Fmoc, see Atherton, E. and Sheppard, R. C. In '*Solid Phase Peptide Synthesis: A Practical Approach*', Oxford University Press, Oxford, U.K. 1989), *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz) or allyloxycarbonyl (Alloc) for example.



15 **Scheme 1.** (a) ^tBuOCOCl, NMM, DCM, -15°C, under argon. (b) Diazomethane in diethyl ether, -15°C, 30mins, then RT overnight. (c) LiCl (10eq) in 80%aq acetic acid RT overnight. (d) HBr / acetic acid followed by re-addition of Pg₂ (if 'Pg₂' is Boc). (e) Rh(II)(OAc)₄, DCM, reflux.

In the illustrated case, condensation with diazomethane provides $Z = \text{CH}_2$ in
 20 general formula (I). Synthesis may commence from a suitably protected β -
 aminoproline (4) which are described in the literature e.g. Gomez-Vidal, J. A. and
 Silverman, R. B. *Org. Lett.*, 3(16), 2481-2484, 2001.

Activation of the suitably protected β -aminoproline (4) via isobutyl chloroformate
25 mixed anhydride, followed by condensation with diazomethane, yields the
diazomethylketone intermediate (5). Treatment of diazomethylketone intermediate
(5) with lithium chloride in aqueous acetic acid provides the protected

-258-

hexahydropyrrolo[3,2-*b*]pyrrol-3-one (6). Alternatively, when Pg₂ is Boc, treatment with HBr in acetic acid provides an intermediate bicycle with the secondary amine. HBr salt. This intermediate may be acylated with a variety of reagents e.g. activated carboxylic acids, sulphonyl chlorides, urethane
5 chloroformates to provide many variations of (6) where the nitrogen substituent is a suitable protecting group 'Pg₂' or R²C(O), R²SO₂, etc. Alternatively, treatment of diazomethylketone intermediate (5) with rhodium (II) tetraacetate in dichloromethane provides the hexahydropyrrolo[3,2-*b*]pyrrol-3-one (6) (e.g. see Lall, M. S. *et al*, *J. Org. Chem.*, 67, 1536-1547, 2002. and refs cited therein).

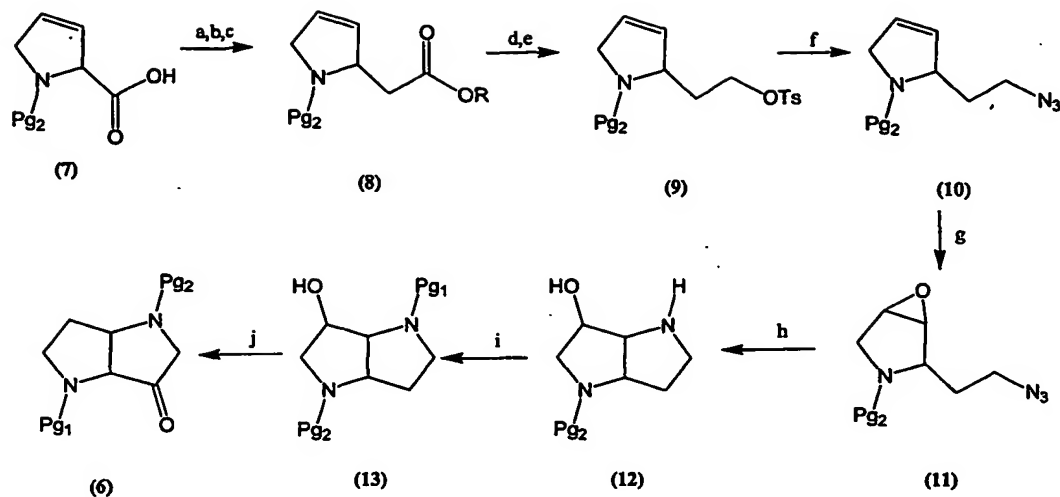
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Introduction of simple 'Z' substituents may be achieved by condensation of activated (4) with alternatives to diazomethane such as diazoethane (Z = CHCH₃, R³ = H, R⁴ = CH₃), or 1-phenyloxydiazoethane (Z = CHCH₂OPh, R³ = H, R⁴ = CH₂OPh).

15

An alternative route towards a suitably protected building block is detailed in Scheme 2. Using an Arndt-Eistert synthesis, a suitably protected 3,4-dehydropyrroline (7) may be homologated by methylene insertion between the α-carbon and carboxylic acid following standard literature methods (e.g. see Meier and Zeller, *Angew. Chem. Intl. Ed. Engl.*, 14, 32-43, 1975 for a review).
20 Conversion of (7) into the α-diazomethylketone proceeds via isobutyl chloroformate mixed anhydride, followed by condensation with diazomethane. Wolff rearrangement, e.g. with silver oxide in methanol provides the protected homologated analogue (8), e.g. 2-Methoxycarbonylmethyl-2,5-dihydro-pyrrole-1-
25 carboxylic acid tert-butyl ester.

-259-



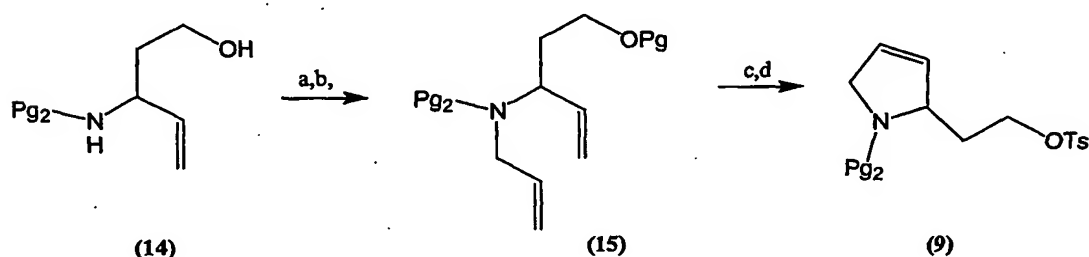
Scheme 2. (a) $t\text{BuOCOC}\text{Cl}$, NMM, DCM, -15°C , under argon. (b) Diazomethane in diethyl ether, -15°C , 30mins, then RT overnight. (c) Arndt-Eistert, e.g. Silver oxide in methanol ($\text{R} = \text{CH}_3$). (d) DIBAL reduction. (e) Tosylchloride, pyridine. (f) Sodium azide, DCM / DMF (g) *m*-chloroperbenzoic acid, DCM. (h) Azide reduction to amine, e.g. Pd-C / H_2 in ethanol. (i) Secondary amine protection, 'Pg₁' e.g. 1.05 eq Fmoc-Cl, 2.1eq Na_2CO_3 , dioxan, water. (j) Dess-Martin periodane, DCM.

Treatment of the methyl ester (8) with a reducing agent such as DIBAL-H (diisobutylaluminium hydride) provides the primary alcohol, which is readily converted to tosylate (9). Similarly the mesylate or triflate analogues of (9) may be prepared. Nucleophilic displacement of the activated alcohol with sodium azide provides intermediate (10) e.g. 2-(2-Azido-ethyl)-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester. Epoxidation of (10) with oxidising agents common to the art such as *m*-CPBA provides the epoxide (11) e.g. 2-(2-Azido-ethyl)-6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester. Reduction of the azide (11) to the amine intermediate may be effected under a range of conditions such as Pd-C / H_2 or triphenylphosphine in THF and water. The amine intermediates undergo intramolecular epoxide ring opening to provide the bicyclic alcohol (12) e.g. 3-Hydroxy-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid tert-butyl ester. The free secondary amine (12) may be protected with a variety of suitable protecting groups such as Fmoc, Boc, Cbz, Alloc to provide orthogonal protection of the bicyclic scaffold. Protected alcohol (13) may be oxidised by reagents common to the art such as pyridine sulphur trioxide

-260-

complex in DMSO and triethylamine or Dess-Martin periodane to provide ketone (6) e.g. 3-Oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1,4-dicarboxylic acid 1-tert-butyl ester 4-(9H-fluoren-9-ylmethyl) ester.

- 5 Alternative routes towards intermediate (9) (ex Scheme 2) are available such as that detailed in Scheme 3. Protected alkene (14) is readily available following literature procedures from the protected homoserine lactol ((a) Wright, D. L. *et al*, *Org. Lett.*, 2(13), 1847-1850, 2000. (b) Boyle, P. H. *et al*, *Tet. Asymm.*, 6, 2819, 1995. (c) Baldwin, J. E. and Flinn, A., *Org. Lett.*, 28, 3605, 1987.). N-alkylation of (14) with a base such as sodium hydride and allyl bromide provides diene (15). Treatment of (15) with the olefin metathesis catalysts developed by Grubbs such as bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride provides the protected primary alcohol intermediate of compound (9) detailed in Scheme 2.

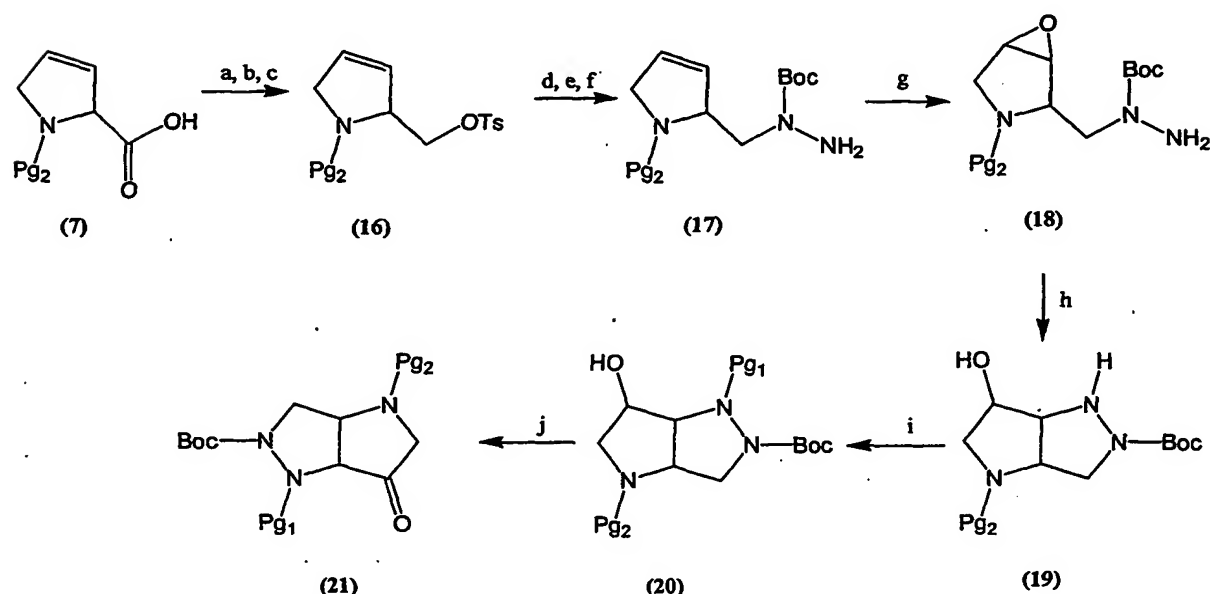


- 15 Scheme 3. (a) Primary alcohol protection, e.g. TBDMS-Cl, base (b) NaH, allylbromide, DMF. (c) bis(tricyclohexylphosphine)benzylidene ruthenium (IV) dichloride, DCM, reflux (d) i. TBAF, THF, ii. Tosylchloride, pyridine.

- 20 The hexahydropyrrolo[3,2-c]pyrazol-6-one (21) scaffold may be prepared following a similar route to that described in Scheme 2 (see Scheme 4). Treatment of the protected 3,4-dehydropoline (7) with HCl in methanol provides the methyl ester. Reduction of the ester with a reducing agent such as DIBAL-H (diisobutylaluminium hydride) provides the primary alcohol, which is readily converted to tosylate (16). Similarly the mesylate or triflate analogues of (16) may be prepared. Nucleophilic displacement of the activated alcohol with a protected hydrazide e.g. Hydrazinecarboxylic acid allyl ester (Alloc-NHNH₂) followed by Boc protection of the secondary hydrazide e.g. under standard Schotten-Baumann
- 25

-261-

conditions and removal of the alloc group e.g. $(PPh_3)_4Pd^0$ / DCM / $PhSiH_3$ provides (17). Epoxidation of (17) with oxidising agents common to the art such as *m*-CPBA provides the epoxide intermediate (18). Intermediate (18) readily undergoes intramolecular epoxide ring opening to provide the bicyclic alcohol (19). The free secondary hydrazide (19) may be protected with a variety of suitable protecting groups e.g. Fmoc, Cbz, Alloc to provide orthogonal protection of the bicyclic scaffold. Protected alcohol (20) may be oxidised by reagents common to the art such as pyridine sulphur trioxide complex in DMSO and triethylamine or Dess-Martin periodane to provide ketone (21).

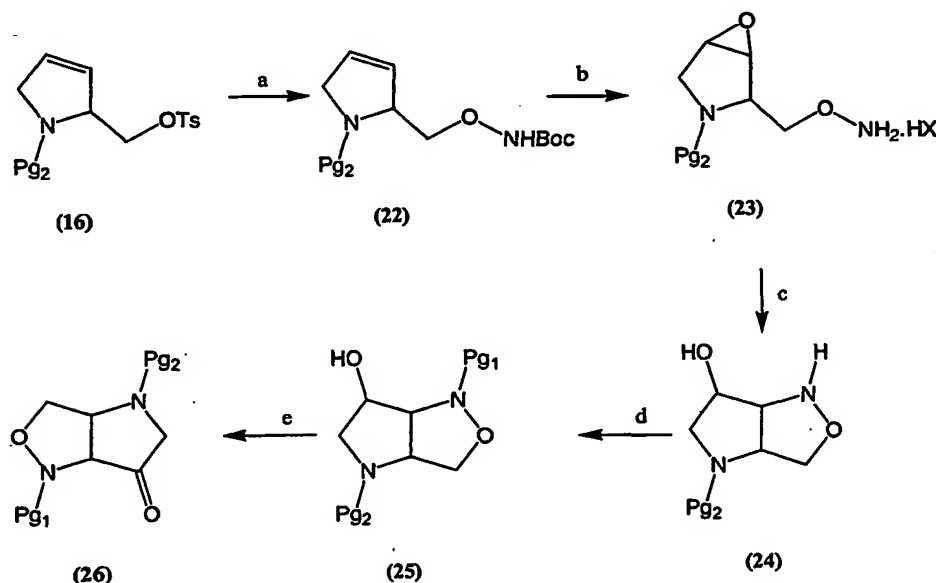


Scheme 4. (a) MeOH / HCl, Dean-Stark (b) DIBAL reduction. (c) Tosylchloride, pyridine (d) Alloc-NHNH₂ (e) (Boc)₂O, Na₂CO₃, dioxan, water (f) $(PPh_3)_4Pd^0$ / DCM / $PhSiH_3$ (g) *m*-chloroperbenzoic acid, DCM. (h) Δ (i) Pg₁ protection, e.g. 1.05 eq Fmoc-Cl, 2.1eq Na₂CO₃, dioxan, water. (j) Dess-Martin periodane, DCM.

The hexahydro-2-oxa-1,4-diazapentalen-6-one (26) scaffold may be prepared following a similar route to that described in Scheme 4. Tosylate (16) undergoes nucleophilic displacement with a protected oxyamine e.g. N-Boc hydroxylamine to provide intermediate (22). Epoxidation of (22) with oxidising agents common to the art such as *m*-CPBA provides the epoxide intermediate, which upon

-262-

acidolytic removal of the Boc group provides intermediate amine.salt (23). Neutralisation of the amine.salt initiates intramolecular epoxide ring opening to provide the bicyclic alcohol (24). The free secondary amine (24) may be protected with a variety of suitable protecting groups e.g. Fmoc, Cbz, Alloc, Boc to provide orthogonal protection of the bicyclic scaffold. Protected alcohol (25) may be oxidised by reagents common to the art such as pyridine sulphur trioxide complex in DMSO and triethylamine or Dess-Martin periodane to provide ketone (26) e.g. 6-Oxo-tetrahydro-2-oxa-1,4-diaza-pentalene-1,4-dicarboxylic acid 4-benzyl ester 1-(9H-fluoren-9-ylmethyl) ester.



Scheme 5. (a) Boc-NHOH (b) i. m-chloroperbenzoic acid, DCM. ii. e.g. HCl / dioxan. (c) Base neutralisation e.g. N-methylmorpholine in DMF. (d) Pg₁ protection, e.g. 1.05 eq Fmoc-Cl, 2.1eq Na₂CO₃, dioxan, water. (e) Dess-Martin periodane, DCM.

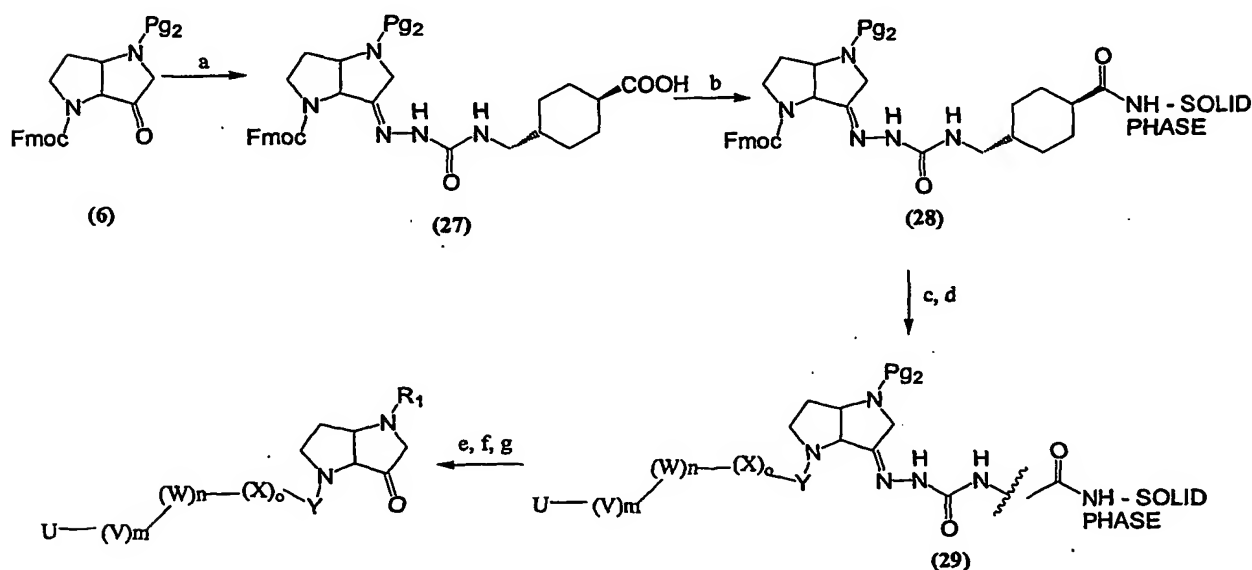
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The protected building blocks detailed in Schemes 1, 2, 4 and 5 may be utilised in a solid phase synthesis of inhibitor molecules (steps (b) to (e)). Preferred protecting group combinations include 'Pg₁' = Fmoc / 'Pg₂' = Boc, or 'Pg₁' = Fmoc / 'Pg₂' = Alloc, or 'Pg₁' = Boc / 'Pg₂' = Fmoc, or 'Pg₁' = Boc / 'Pg₂' = Alloc, or 'Pg₁' = Alloc / 'Pg₂' = Fmoc, or 'Pg₁' = Alloc / 'Pg₂' = Boc. The solid phase syntheses exemplified in Schemes 6 and 7 by the use of

20

-263-

hexahydropyrrolo[3,2-*b*]pyrrol-3-one (6) and octahydropyrrolo[3,2-*b*]pyrrol-3-ol (13) could equally apply to ketones (21) and (26) and alcohols (20) and (25). Step (b), the solid phase linkage of an aldehyde or ketone, has previously been described by a variety of methods (e.g. see (a) James, I. W., 1999, (b) Lee, A., Huang, L., Ellman, J. A., *J. Am. Chem. Soc.*, **121**(43), 9907-9914, 1999, (c) Murphy, A. M., *et al.*, *J. Am. Chem. Soc.*, **114**, 3156-3157, 1992). A suitable method amenable to the reversible linkage of an alkyl ketone functionality such as (6) is through a combination of the previously described chemistries. The semicarbazide, 4-[[[(hydrazinocarbonyl)amino]methyl]cyclohexane carboxylic acid, trifluoroacetate (Murphy, A. M., *et al.*, *J. Am. Chem. Soc.*, **114**, 3156-3157, 1992), may be utilised as illustrated in Scheme 6, where 'Pg₁' = Fmoc and 'Pg₂' = Boc or Alloc, exemplified by linkage of the hexahydropyrrolo[3,2-*b*]pyrrol-3-one (6).



15

Scheme 6. (a) (6) in 90% EtOH / H₂O / NaOAc / 4-[[[(hydrazinocarbonyl)amino]methyl]-cyclohexane carboxylic acid.trifluoroacetate, reflux. (b) 3eq construct (27) / 3eq HBTU / 3eq HOBt / 6eq NMM, NH₂-SOLID PHASE, DMF, RT, o/n. (c) 20% piperidine / DMF, RT, 30mins. (d) Range of chemistries to add U-V-W-X-Y. (e) 'Pg₂' = Boc then 35%TFA in DCM, or 'Pg₂' = Alloc then e.g. (PPh₃)₄Pd(0) catalysed deprotection /CHCl₃ / DMF / AcOH / NMM (f) i. RCOOH /

20

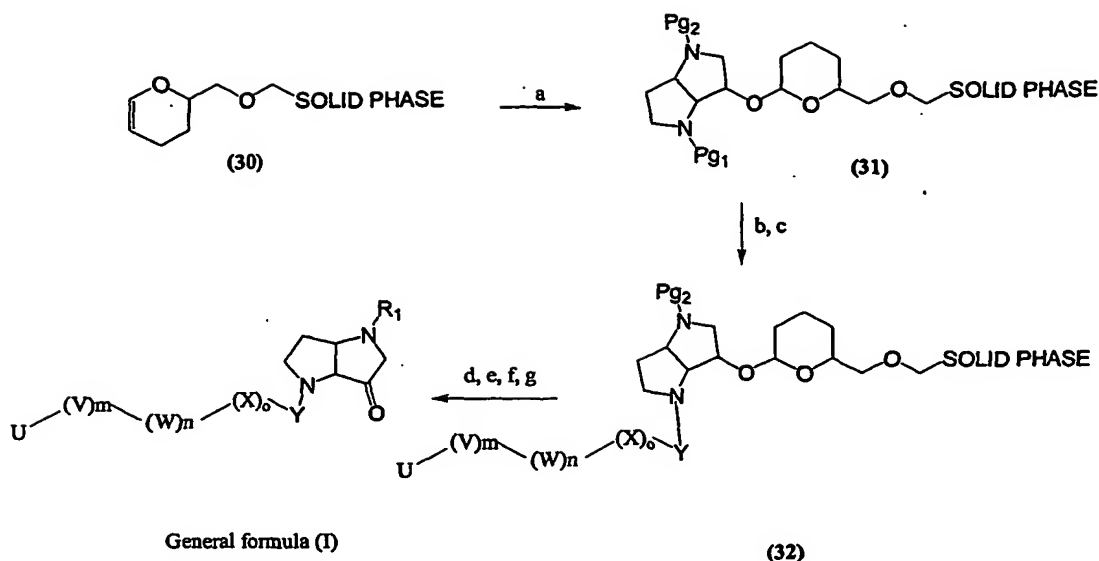
-264-

activation e.g. HBTU / HOBT / NMM, in DMF or ii. SO₂Cl, pyridine in DMF. (g) 95% TFA / H₂O.

Construct (28) is prepared through reaction of the linker molecule (27) and the
5 hexahydropyrrolo[3,2-*b*]pyrrol-3-one (6) by reflux in aqueous ethanol / sodium
acetate. Standard solid phase techniques (e.g. see Atherton, E. and Sheppard, R.
C. In '*Solid Phase Peptide Synthesis: A Practical Approach*', Oxford University
Press, Oxford, U.K. 1989) are used to anchor the construct to an amino-
functionalised solid phase through the free carboxylic acid functionality of (27),
10 providing the loaded construct (28). Loaded construct (28) may be reacted with a
wide range of carboxylic acids or sulphonyl chlorides available commercially in
the literature, to introduce the left-hand portion 'U-V-W-X-Y' in general formula
(I), providing loaded construct (29). Orthogonal removal of 'Pg₂' then liberates
the secondary amine functionality of the right-hand ring, which may be acylated
15 with a range of carboxylic acid and sulphonyl chlorides. Finally, compounds of
general formula (I) are released from the solid phase by treatment with 95% aq
trifluoroacetic acid.

An alternative solid phase synthesis of compounds of general formula (I) utilises
20 the bicyclic alcohol intermediate (13), Scheme 7. The secondary alcohol may be
attached to the solid phase through the acid labile dihydropyran linker (30) that is
well known in the literature (e.g. see (a) Thompson, L. A. and Ellman, J. A., *Tet.*
Lett., 35, 9333, 1994. (b) Kick, E. K. and Ellman, J. A. *J. Med. Chem.*, 38, 1427,
1995.). Preferred protecting group combinations include 'Pg₁' = Fmoc / 'Pg₂' =
25 Alloc, or 'Pg₁' = Alloc / 'Pg₂' = Fmoc.

-265-

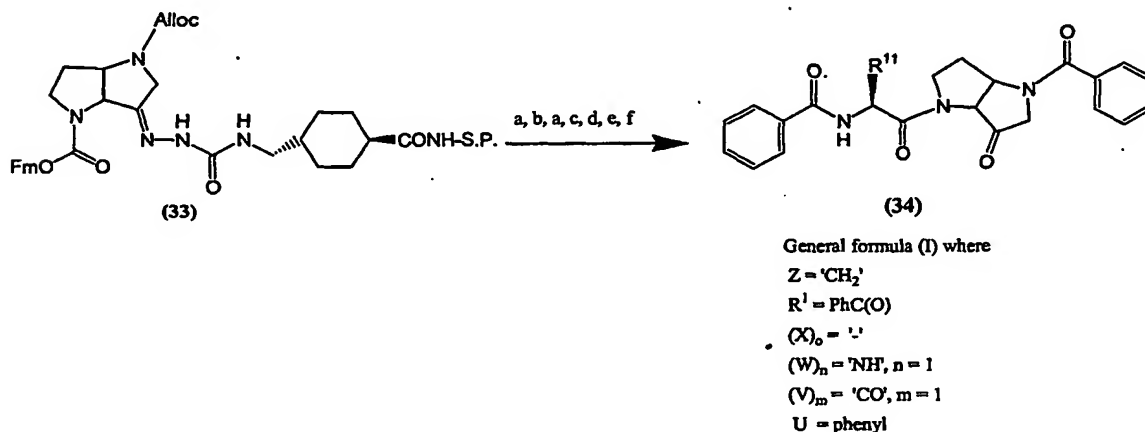


Scheme 7. (a) (13) in dichloroethane, pyridinium p-toluenesulphonate, reflux (b) 'Pg₁' = Fmoc then 20% piperidine / DMF, RT, 30mins or 'Pg₁' = Alloc then (PPh₃)₄Pd(0) catalysed deprotection /CHCl₃ / DMF / AcOH / NMM (c) Range of chemistries to add U-V-W-X-Y. (d) 'Pg₂' = Fmoc then 20% piperidine / DMF, RT, 30mins or 'Pg₂' = Alloc then e.g. (PPh₃)₄Pd(0) catalysed deprotection /CHCl₃ / DMF / AcOH / NMM (e) i. RCOOH / activation e.g. HBTU / HOBT / NMM, in DMF or ii. SO₂Cl, pyridine in DMF. (f) 95% TFA / H₂O. (g) Solid supported oxidation or e.g. Dess-Martin periodane, DCM.

Loaded construct (31) may be reacted with a wide range of carboxylic acids or sulphonyl chlorides available commercially in the literature, to introduce the left-hand portion 'U-V-W-X-Y' in general formula (I), providing loaded construct (32). Orthogonal removal of 'Pg₂' then liberates the secondary amine functionality of the right-hand ring, which may be acylated with a range of carboxylic acid and sulphonyl chlorides. Compounds of general formula (I) are released from the solid phase by treatment with 95% aq trifluoroacetic acid and the resultant alcohols may be oxidised with a range of solution based reagents e.g. Dess-Martin periodane in DCM or solid supported oxidants (e.g. see Ley, S. V. *et al*, *J. Chem. Soc. Perkin Trans. 1.*, 3815-4195, 2000.) to provide the ketone products.

-266-

In the simplest example, the entire left hand portion of an inhibitor of general formula (I) comprises a capped aminoacid (Scheme 8), providing for example analogues of general formula (I) where $Z = \text{'CH}_2\text{'}$, $Y = \text{CHR}^{11}\text{C(O)}$, $(X)_o = \text{'-'}\text{'}$, $(W)_n = \text{'NH'}$, $R^{18} = \text{'H'}$, $n = 1$, $(V)_m = \text{'CO'}$, $m = 1$ and $U = \text{phenyl}$. Scheme 8 details chemistry utilising protected ketone construct (33) and the reactions could equally be applied to the protected alcohol construct (31).

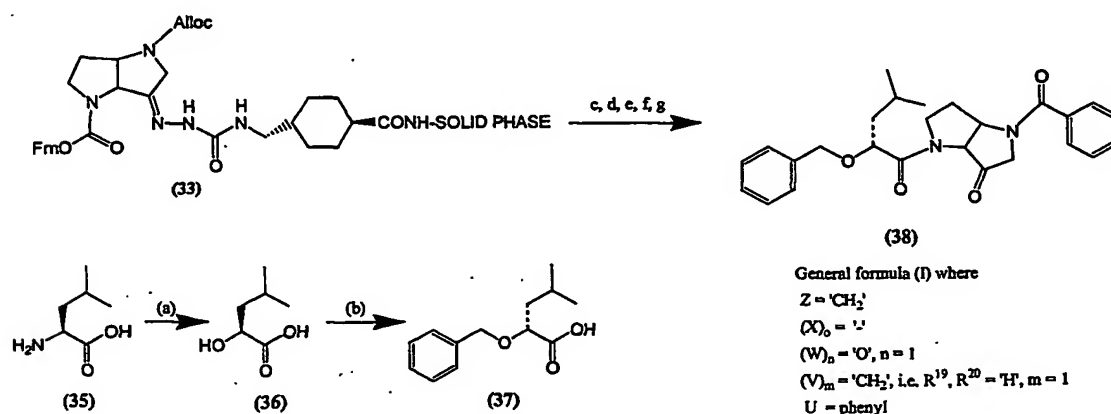


Scheme 8. (a) 20% piperidine / DMF, 30mins (b) 20eq Fmoc-aminoacid / 20eq HBTU / 20eq HOBT / 40eq NMM, DMF, o/n (c) 5eq carboxylic acid / 5eq HBTU / 5eq HOBT / 10eq NMM, DMF, RT, o/n (d) Deprotection of Pg_2 Alloc; e.g. TMS-N_3 / TBAF / $(\text{PPh}_3)_4\text{Pd}^0$ / under N_2 . (e) 20eq Benzoic acid / 20eq HBTU / 20eq HOBT / 40eq NMM, DMF, RT, o/n (f) TFA / H_2O (95:5, v/v), RT.

Alternatively, carboxylic acids can be prepared in solution by traditional organic chemistry methods and coupled to constructs (28) and (31) on the solid phase (Schemes 9-13). For example (Scheme 9), treatment in solution of an amino acid, exemplified by (35) with sodium nitrite / H_2SO_4 , provides the α -hydroxyacid, exemplified by (36) (Degerbeck, F. *et al*, *J. Chem. Soc, Perkin Trans. 1*, 11-14, 1993). Treatment of α -hydroxyacid, (36) with sodium hydride in a dimethylformamide / dichloromethane mixture followed by addition of benzyl bromide, provides (*RS*) 2-benzyloxy-4-methyl-pentanoic acid (37). Coupling of (37) to the solid phase construct (33) followed by alloc deprotection, benzoylation then cleavage, provides (38), an example of general formula (I) where $Z = \text{'CH}_2\text{'}$, $(X)_o = \text{'-'}\text{'}$, $(W)_n = \text{'O'}$, $n = 1$, $(V)_m = \text{'CH}_2\text{'}$, $m = 1$, R^{19} and $R^{20} = \text{H}$ and $U =$

-267-

phenyl. To those skilled in the practices of organic synthesis, a wide variety of aminoacids such as (35) may be converted to the corresponding α -hydroxyacid such as (36) following the general conditions detailed. Additionally, benzylbromide may be replaced by any reasonable $\text{Ar-CR}^{19}\text{R}^{20}$ -halide, providing many variations of carboxylic acid (37) following the general conditions detailed. In certain instances, it may be advantageous to temporarily protect the carboxylic acid as the methyl ester (for example compound (43), Scheme 11) prior to reaction with the alkylhalide. The ester intermediate is then simply hydrolysed to acid (37). Analogues of (38), exploring a wide range of $(V)_m$ and U in general formula (I) may be prepared through the general conditions detailed in Scheme 9.



Scheme 9. (a) $\text{NaNO}_2 / \text{H}_2\text{SO}_4$, $0^\circ\text{C} \rightarrow \text{RT}$, 2hr (b) 2.3eq NaH, 1:1 DMF / DCM, 1.4eq benzylbromide, o/n (c) 20% piperidine / DMF, 30mins. (d) 10eq (37) / 10eq HBTU / 10eq HOBt / 20eq NMM, DMF, RT, o/n (e) Deprotection of Pg_2 Alloc; e.g. TMS- N_3 / TBAF / $(\text{PPh}_3)_4\text{Pd}^0$ / under N_2 . (f) 20eq Benzoic acid / 20eq HBTU / 20eq HOBt / 40eq NMM, DMF, RT, o/n (g) TFA / H_2O (95:5, v/v), RT.

Since the final synthetic step involves a trifluoroacetic acid (TFA) mediated cleavage of the solid phase bound compound, analogues where the substituted ether is labile to TFA may be prepared in solution by an alternative route (see Scheme 16).

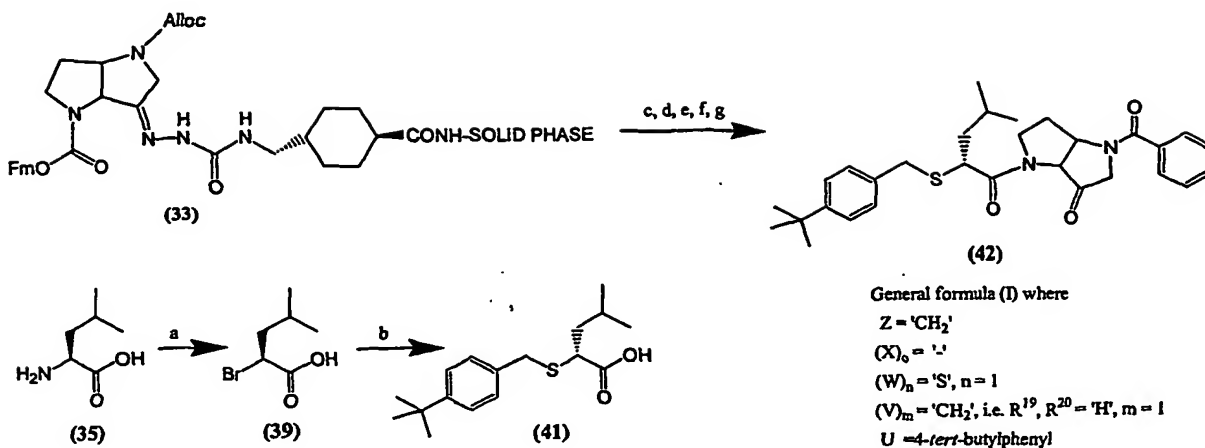
Alternatively, coupling of construct (33) (following removal of Fmoc) with the α -hydroxyacid (36), provides a versatile solid phase bound intermediate 'Y'

-268-

substituent in general formula (I) that may be reacted with many reagents. For example, the α -hydroxyl can be reacted under Mitsunobu conditions (Hughes, D. L. *Org. React.(N.Y)*, 42, 335-656, 1992) to give ethers (i.e. X = '-', W = 'O', in general formula (I)) (see Grabowska, U. *et al*, *J. Comb. Chem.*, 2(5), 475-490, 2000, for an example of Mitsunobu reaction on the solid phase). Alternatively, the α -hydroxyl can be reacted with a carbamoyl chloride to give a carbamate (i.e. X = '-', W = 'O', V = 'NHC(O)', in general formula (I)).

Alternatively, (Scheme 10), treatment in solution of an amino acid, exemplified by (35) with sodium nitrite / H₂SO₄ / potassium bromide provides the α -bromoacid, exemplified by (39) (Souers, A. J. *et al*, *Synthesis*, 4, 583-585, 1999) with retention of configuration. Treatment of α -bromoacid (39) with an alkylthiol exemplified by 4-*tert*-butylphenylmethanethiol (40) in dimethylformamide / triethylamine, provides 2*R*-(4-*tert*-butylbenzylsulfanyl)-4-methylpropionic acid (41), with inversion of configuration. Coupling of (41) to the solid phase construct (33) followed by alloc deprotection, benzoylation, then cleavage provides (42), an example of general formula (I) where Z = 'CH₂', (X)_o = '-', (W)_n = 'S', n = 1, (V)_m = 'CH₂', m = 1, R¹⁹ and R²⁰ = H and U = 4-*tert*-butylphenyl. To those skilled in the practices of organic synthesis, a wide variety of aminoacids such as (35) may be converted to the corresponding α -bromoacid such as (39) following the general conditions detailed. Additionally, starting with the *R*-isomer of (35) gives the *R*-bromoacid analogue of (39) and *S*-thioether analogue of (41). Additionally, (4-*tert*-butylphenyl)methanethiol (40) may be replaced by any reasonable Ar-CR¹⁹R²⁰-SH, providing many variations of carboxylic acid (41) following the general conditions detailed. Thus analogues of (42) exploring a wide range of (V)_m and U in general formula (I) may be prepared through the general conditions detailed in Scheme 10.

-269-



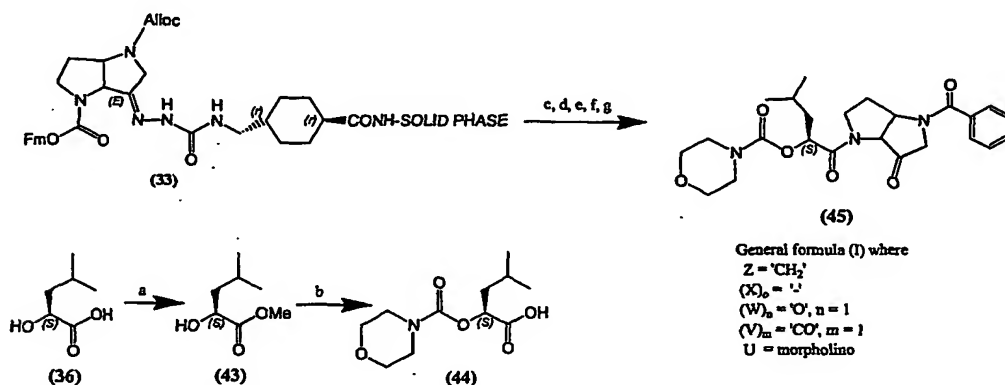
5 **Scheme 10.** (a) NaNO₂ / H₂SO₄, KBr 0°C → RT, 2hr (b) Alkylthiol (40) / DMF / NEt₃, o/n (c) 20% piperidine / DMF, 30mins. (d) 10eq (41) / 10eq HBTU / 10eq HOBt / 20eq NMM, DMF, RT, o/n (e) Deprotection of Pg₂ Alloc; e.g. TMS-N₃ / TBAF / (PPh₃)₄Pd⁰ / under N₂. (f) 20eq Benzoic acid / 20eq HBTU / 20eq HOBt / 40eq NMM, DMF, RT, o/n (g) TFA / H₂O (95:5, v/v), RT.

10 Alternatively, coupling of construct (33) (following removal of Fmoc) with an α-bromoacid e.g. (39), provides a versatile intermediate 'Y' substituent in general formula (I) that may be reacted with many reagents. For example, the α-bromide can be displaced with nucleophiles e.g. alcohols, thiols, carbanions etc, to give ethers (i.e. X = '-', W = 'O', in general formula (I)), thioethers (i.e. X = '-', W = 'S', in general formula (I)). The thioethers may optionally be oxidised to the sulphone (see Scheme 14, i.e. X = '-', W = 'SO₂', in general formula (I)) (see Grabowska, U. *et al*, *J. Comb. Chem.*, 2(5), 475-490, 2000, for an example of bromide displacement and thioether oxidation on the solid phase).

20 Alternatively, (Scheme 11), treatment of an α-hydroxyacid, exemplified by (36) with trimethylsilylchloride and methanol provides the methyl ester (43). Activation of the free hydroxyl to the chloroformate with phosgene in dichloromethane followed by addition of morpholine, then hydrolysis, provides morpholine-4-carboxylic acid 1-carboxy-3-methyl-butyl ester (44). Coupling of (44) to the solid phase construct (33) followed by alloc deprotection, benzoylation

-270-

then cleavage provides (45), an example of general formula (I) where $Z = 'CH_2'$, $(X)_o = '-'$, $(W)_n = 'O'$, $n = 1$, $(V)_m = 'CO'$ and $U = \text{morpholino}$. To those skilled in the practices of organic synthesis, a wide variety of α -hydroxyacid esters such as (36) could be converted to the activated chloroformate following the general conditions detailed. Additionally, morpholine may be replaced by any reasonable amine, providing many variations of carboxylic acid (44) following the general conditions detailed. Thus analogues of (45) exploring a wide range of $(V)_m$ and U in general formula (I) may be prepared through the general conditions detailed in Scheme 11.

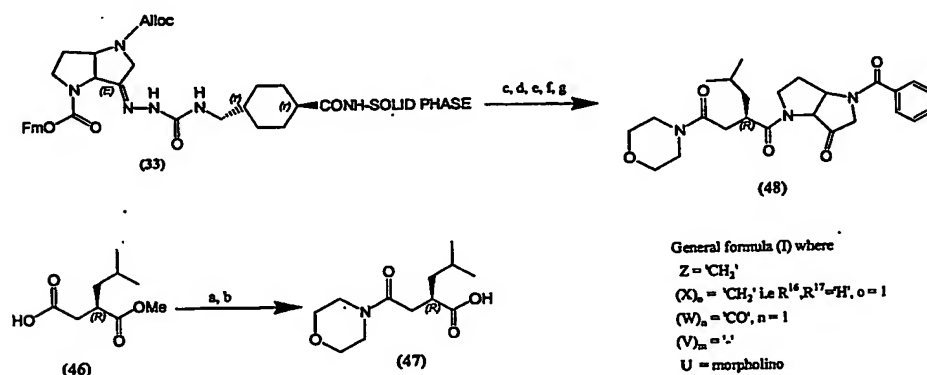


Scheme 11. (a) Me_3SiCl , MeOH, RT, o/n. (b) i. $COCl_2$ / DCM / o/n, ii. Morpholine / DCM $0^\circ C$, 2hr, iii. LiOH in H_2O / dioxan, $0^\circ C$. (c) 20% piperidine / DMF, 30mins. (d) 10eq (44) / 10eq HBTU / 10eq HOBt / 20eq NMM, DMF, RT, o/n. (e) Deprotection of Pg_2 Alloc; e.g. TMS- N_3 / TBAF / $(PPh_3)_4Pd^0$ / under N_2 . (f) 20eq Benzoic acid / 20eq HBTU / 20eq HOBt / 40eq NMM, DMF, RT, o/n. (g) TFA / H_2O (95:5, v/v), RT.

Alternatively, (Scheme 12), a wide range of alkylsuccinate esters exemplified by 2*R*-isobutyl-succinic acid 1-methyl ester (46) are commercially available or readily prepared by known methods (see (a) Azam *et al*, *J. Chem. Soc. Perkin Trans. 1*, 621-, 1996; (b) Evans *et al*, *J. Chem. Soc. Perkin Trans. 1*, 103, 2127, 1981; (c) Oikawa *et al*, *Tet. Lett.*, 37, 6169, 1996). Carboxyl activation of alkylsuccinate ester (46) followed by addition of morpholine in dimethylformamide and subsequent ester hydrolysis, provides 4-Methyl-2*R*-(2-morpholin-4-yl-2-oxo-ethyl)-pentanoic acid (47). Coupling of (47) to the solid phase construct (33) followed by alloc deprotection, benzoylation then cleavage

-271-

provides (48), an example of general formula (I) where $Z = 'CH_2'$, $(X)_o = 'CH_2'$, $(W)_n = 'CO'$, $n = 1$, $(V)_m = '-'$ and $U = \text{morpholino}$. To those skilled in the practices of organic synthesis, a wide variety of alkylsuccinate esters such as (46) may be prepared and converted to the corresponding substituted alkylsuccinate acid such as (47) following the general conditions detailed. Additionally, morpholine may be replaced by any reasonable amine, providing many variations of carboxylic acid (47) following the general conditions detailed. Thus analogues of (48) exploring a wide range of $(X)_o$, $(V)_m$ and U in general formula (I) may be prepared through the general conditions detailed in Scheme 12.

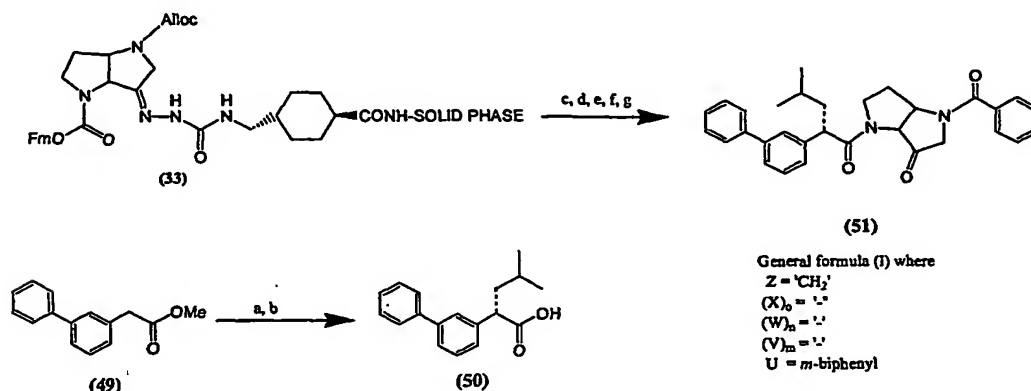


Scheme 12. (a) i.EDC / 1-hydroxybenzotriazole /DMF, 0°C, 30mins. ii. Morpholine, RT, o/n (b) LiOH in H₂O / dioxan, 0°C (c) 20% piperidine / DMF, 30mins. (d) 10eq (47) / 10eq HBTU / 10eq HOBt / 20eq NMM, DMF, RT, o/n. (e) Deprotection of Pg₂ Alloc; e.g. TMS-N₃ / TBAF / (PPh₃)₄Pd⁰ / under N₂. (f) 20eq Benzoic acid / 20eq HBTU / 20eq HOBt / 40eq NMM, DMF, RT, o/n. (g) TFA / H₂O (95:5, v/v), RT.

Alternatively, (Scheme 13), a wide range of biarylalkylacetic acids, exemplified by 2*RS*-biphenyl-3-yl-4-methylpentanoic acid (50) are readily available by known methods (see (a) DesJarlais, R. L. *et al*, *J. Am. Chem. Soc.*, **120**, 9114-9115, **1998**; (b) Oballa, R. M. *et al*, WO 0149288). Coupling of biarylalkylacetic acid (50) to the solid phase construct (33) followed by alloc deprotection, benzylation then cleavage provides (51), an example of general formula (I) where $Z = 'CH_2'$, $(X)_o = '-'$, $(W)_n = '-'$, $(V)_m = '-'$ and $U = m\text{-biphenyl}$. To those skilled in the practices of organic synthesis, a wide variety of biarylalkylacetic acids such as (50) may be

-272-

prepared by alkylation of the α -anion of the free acid analogue of (49), which in turn is prepared by Suzuki coupling of phenylboronic acid and 3-bromophenylacetic acid methyl ester. Phenylboronic acid may be replaced by a wide range of arylboronic acids in the Suzuki coupling, providing many variations of carboxylic acid (50) following the general conditions detailed. Thus analogues of (51) exploring a wide range of group 'U' in general formula (I) may be prepared through the general conditions detailed in Scheme 13.



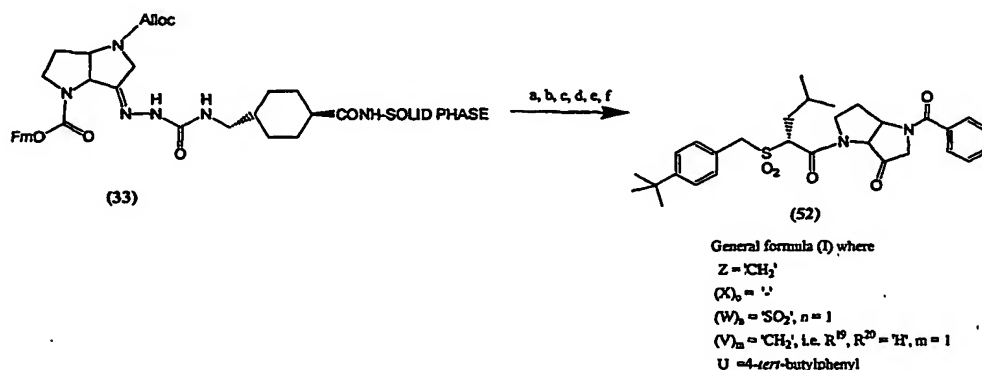
Scheme 13. (a) LiOH in H₂O / dioxan, 0°C (b) i.LDA, THF, 2-methylpropenylbromide. ii. Pd/C, EtOH, H₂ (c) 20% piperidine / DMF, 30mins. (d) 10eq (50) / 10eq HBTU / 10eq HOBT / 20eq NMM, DMF, RT, o/n. (e) Deprotection of Pg₂ Alloc; e.g. TMS-N₃ / TBAF / (PPh₃)₄Pd⁰ / under N₂. (f) 20eq Benzoic acid / 20eq HBTU / 20eq HOBT / 40eq NMM, DMF, RT, o/n. (g) TFA / H₂O (95:5, v/v), RT.

Many other possibilities for solid phase organic chemistry (e.g. see Brown, R. D. *J. Chem. Soc., Perkin Trans.1*, **19**, 3293-3320, 1998, for a review of recent SPOC publications) can be used to derivatise constructs (28) and (31) towards compounds of general formula (I). For example, the left-hand portion 'U-V-W-X-Y' in general formula (I) can be partially constructed in solution, coupled to constructs (28) and (31) and further modified on the solid phase. For example (Scheme 14), a simple extension of Scheme 10 is through the oxidation of the intermediate solid phase bound species, with *m*-chloroperbenzoic acid in dichloromethane prior to cleavage, to give the sulphone analogue. Commencing from 2*R*-(4-*tert*-butylbenzyl)sulfanyl-4-methylpropionic acid (41), sulphone (52)

-273-

is prepared, an example of general formula (I) where $Z = \text{'CH}_2\text{'}$, $(X)_o = \text{'-'}\text{'}$, $(W)_n = \text{'SO}_2\text{'}$, $n = 1$, $(V)_m = \text{'CH}_2\text{'}$, $m = 1$, R^{19} and $R^{20} = \text{H}$ and $U = 4\text{-}tert\text{-butylphenyl}$. As described in Scheme 10, many variations of carboxylic acid (41) may be prepared following the general conditions detailed. Thus analogues of (52)

5 exploring a wide range of $(V)_m$ and U in general formula (I) may be prepared through the general conditions detailed in Schemes 10 and 14.



Scheme 14. (a) 20% piperidine / DMF, 30mins. (b) 10eq (41) / 10eq HBTU / 10eq HOBT / 20eq NMM, DMF, RT, o/n. (c) Deprotection of Pg_2 Alloc; e.g. TMS- N_3 / TBAF / $(\text{PPh}_3)_4\text{Pd}^0$ / under N_2 . (d) 20eq Benzoic acid / 20eq HBTU / 20eq HOBT / 40eq NMM, DMF, RT, o/n. (e) 5eq *m*-chloroperbenzoic acid / DCM, RT, 5hr. (f) TFA / H_2O (95:5, v/v), RT.

Compounds of general formula (I) are finally released from the solid phase by treatment with trifluoroacetic acid / water, followed by evaporation, lyophilis and standard analytical characterisation.

A second strategy for the synthesis of compounds of general formula (I) comprises:-

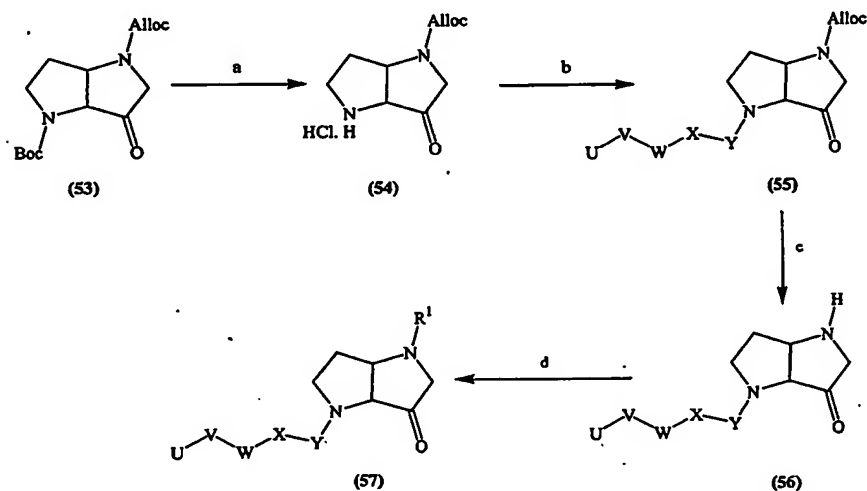
(a) Preparation of an appropriately functionalised and protected hexahydropyrrolo[3,2-*b*]pyrrol-3-one, hexahydropyrrolo[3,2-*c*]pyrazol-6-one or hexahydro-2-oxa-1,4-diazapentalen-6-one building block in solution.

-274-

Preferred protecting groups for solution phase chemistry are the 9-fluorenylmethoxycarbonyl, $N\alpha$ -*tert*-butoxycarbonyl, $N\alpha$ -benzyloxy carbonyl and $N\alpha$ -allyloxycarbonyl group.

- 5 (b) Standard organic chemistry methods for the conversion of building block (a) towards compounds of general formula (I).

In the simplest example, the entire left hand portion of an inhibitor of general formula (I) can be prepared in solution by traditional organic chemistry methods and coupled to building block (a) (see Scheme 15 exemplified by the use of 3-Oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carboxylic acid allyl ester (54)).



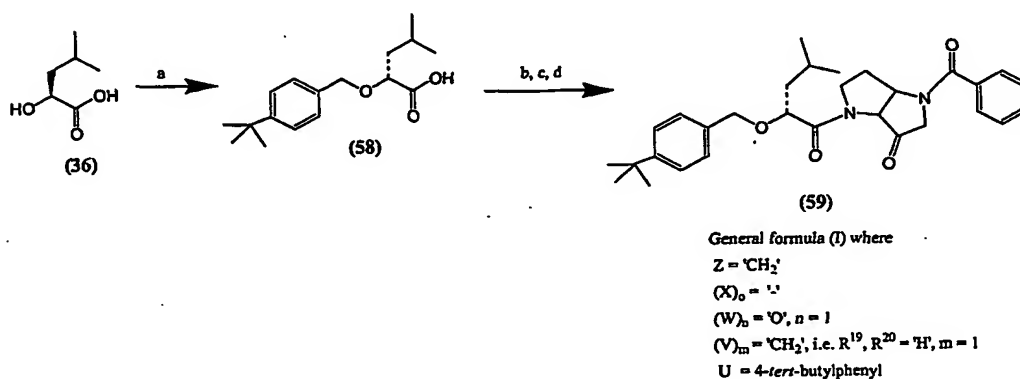
15 Scheme 15. (a) 4M HCl in dioxan, 0°C. (b) Pre-prepared U-V-W-X-Y-COOH / activation e.g. HATU / HOAt / NMM, DMF, RT, o/n. (c) Alloc deprotection e.g. (PPh₃)₄Pd⁰ / DCM / PhSiH₃ (d) Acylation e.g. RCOOH, ^tBuOCOC₂H₅, NMM, DCM, or SO₂Cl₂ / Pyridine.

The general strategy detailed in Scheme 15 is particularly useful when the compound of general formula (I) contains a substituent that is labile to trifluoroacetic acid, this being the final reagent used in each of the solid phase Schemes 6-14. For example (Scheme 16), treatment in solution of α -hydroxyacid (36) with sodium hydride in a dimethylformamide / dichloromethane mixture followed by addition of 4-*tert*-butylbenzyl bromide, provides 2*RS*-(4-*tert*-

-275-

butylbenzyloxy)-4-methylpentanoic acid (58). Coupling of (58) to hydrochloride salt (54), followed by alloc deprotection then benzylation provides (59), an example of general formula (I) where $Z = 'CH_2'$, $(X)_0 = '-'$, $(W)_n = 'O'$, $n = 1$, $(V)_m = 'CH_2'$, $m = 1$, R^{19} and $R^{20} = H$ and $U = 4\text{-}tert\text{-butylphenyl}$. To those skilled in the practices of organic synthesis, 4-*tert*-butylbenzyl bromide may be replaced by any reasonable $Ar-CR^{19}R^{20}$ -halide, providing many variations of carboxylic acid (58) under the conditions shown. Thus analogues of (59) exploring a wide range of $(V)_m$ and U in general formula (I) may be prepared through the conditions detailed in Scheme 16.

10



Scheme 16. (a) 2.2eq NaH, 1:1 DMF / DCM, 1.25eq 4-*tert*-benzylbromide. (b) 1eq (58), 1eq $t\text{BuOCOC}$ l, 2eq NMM, DCM, -15°C , 1hr, under nitrogen, then 1eq, (54), RT, o/n. (c) Alloc deprotection e.g. $(PPh_3)_4Pd^0$ / DCM / $PhSiH_3$ (d) Acylation e.g. $RCOOH$, $t\text{BuOCOC}$ l, NMM, DCM, or SO_2Cl / Pyridine.

15

A third strategy for the synthesis of compounds of general formula (I) where the addition of U-V-W-X-Y to the protected building block involves multistep organic reactions comprises:-

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- (a) Preparation of an appropriately functionalised and protected hexahydropyrrolo[3,2-*b*]pyrrol-3-one, hexahydropyrrolo[3,2-*c*]pyrazol-6-one or hexahydro-2-oxa-1,4-diazapentalen-6-one building block in solution.

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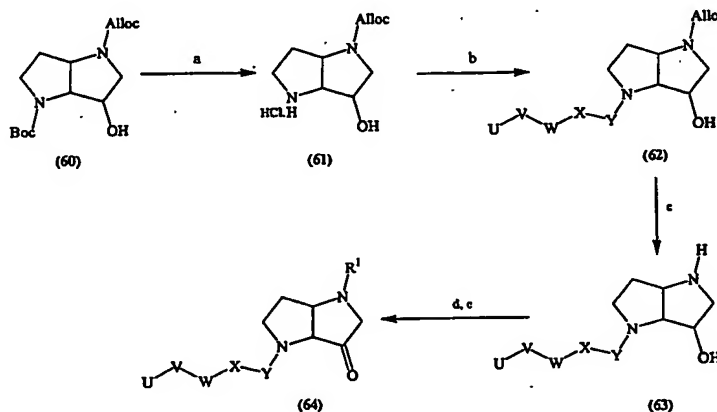
-276-

Preferred protecting groups for solution phase chemistry are the 9-fluorenylmethoxycarbonyl, $N\alpha$ -*tert*-butoxycarbonyl, $N\alpha$ -benzyloxy carbonyl and $N\alpha$ -allyloxycarbonyl group.

(b) Protection of the ketone functionality of the hexahydropyrrolo[3,2-*b*]pyrrol-3-one, hexahydropyrrolo[3,2-*c*]pyrazol-6-one or hexahydro-2-oxa-1,4-diazapentalen-6-one building block e.g. as a dimethylacetal. Alternatively, the reduced ketone (achiral secondary alcohols (13), (20) and (25)) intermediates may be used and re-oxidised as the final synthetic step.

(c) Standard organic chemistry methods for the conversion of building block (b) towards compounds of general formula (I).

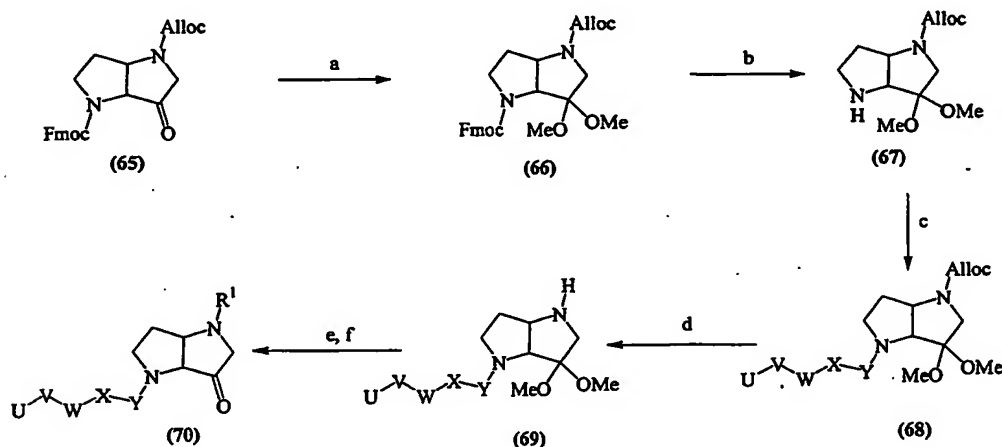
Intermediates may be prepared in solution, followed by coupling to building block (b) and further derivitisation towards compounds of general formula (I) (see Scheme 17 exemplified by preparation and use of the 3-Hydroxy-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid allyl ester (61)).



Scheme 17. (a) 4M HCl in dioxan, 0°C. (b) Stepwise reaction with intermediates of Y, then X, then W etc., to stepwise construct compounds (62). (c) Alloc deprotection e.g. $(PPh_3)_4Pd^0$ / DCM / $PhSiH_3$ (d) Acylation e.g. $RCOOH$, $tBuOCOCl$, NMM, DCM, or SO_2Cl / Pyridine. (e) Oxidation, e.g. Dess-Martin periodane, CH_2Cl_2 .

-277-

Alternatively, depending upon the types of chemistry used to construct the left hand side U-V-W-X-Y of compounds of general formula (I), the ketone may require protection e.g. as the dimethyl acetal. Such a method is detailed and exemplified in Scheme 18 by the preparation and use of 3,3-Dimethoxy-



Scheme 18. (a) Triethylorthoformate / pTSA / MeOH. (b) Fmoc deprotection, e.g. Solid supported piperidine / DMF (c) Stepwise reaction with intermediates of Y, then X, then W etc., to stepwise construct compounds (68). (d) Alloc deprotection e.g. (PPh₃)₄Pd⁰ / DCM / PhSiH₃ (e) Acylation e.g. RCOOH, ^tBuOCOCl, NMM, DCM, or SO₂Cl / Pyridine. (f) Trifluoroacetic acid / CH₂Cl₂ / H₂O.

The invention extends to novel intermediates as described above, and to processes for preparing compounds of general formula (I) from each of their immediate precursors. In turn, processes for preparing intermediates from their immediate precursors also form part of the invention.

Compounds of general formula (I) are useful both as laboratory tools and as therapeutic agents. In the laboratory certain compounds of the invention are useful in establishing whether a known or newly discovered cysteine protease contributes a critical or at least significant biochemical function during the establishment or progression of a disease state, a process commonly referred to as 'target validation'.

-278-

According to a second aspect of the invention, there is provided a method of validating a known or putative cysteine protease inhibitor as a therapeutic target, the method comprising:

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(a) assessing the *in vitro* binding of a compound as described above to an isolated known or putative cysteine protease, providing a measure of potency; and optionally, one or more of the steps of:

10

(b) assessing the binding of the compound to closely related homologous proteases of the target and general house-keeping proteases (e.g. trypsin) to provides a measure of selectivity;

15

(c) monitoring a cell-based functional marker of a particular cysteine protease activity, in the presence of the compound; and

(d) monitoring an animal model-based functional marker of a particular cysteine protease activity in the presence of the compound.

20

The invention therefore provides a method of validating a known or putative cysteine protease inhibitor as a therapeutic target. Differing approaches and levels of complexity are appropriate to the effective inhibition and 'validation' of a particular target. In the first instance, the method comprises assessing the *in vitro* binding of a compound of general formula (I) to an isolated known or putative cysteine protease, providing a measure of 'potency'. An additional assessment of the binding of a compound of general formula (I) to closely related homologous proteases of the target and general house-keeping proteases (e.g. trypsin) provides a measure of 'selectivity'. A second level of complexity may be assessed by monitoring a cell-based functional marker of a particular cysteine protease activity, in the presence of a compound of general formula (I). For example, a 'human osteoclast resorption assay' has been utilised as a cell-based secondary *in vitro* testing system for monitoring the activity of cathepsin K and the biochemical

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-279-

effect of protease inhibitors (e.g. see WO-A-9850533). An 'MHC-II processing – T-cell activation assay' has been utilised as a cell-based secondary *in vitro* testing system for monitoring the activity of cathepsin S and the biochemical effect of protease inhibitors (Shi, G-P., *et al*, *Immunity*, 10, 197-206, 1999). When
5 investigating viral or bacterial infections such a marker could simply be a functional assessment of viral (e.g. count of mRNA copies) or bacterial loading and assessing the biochemical effect of protease inhibitors. A third level of complexity may be assessed by monitoring an animal model-based functional marker of a particular cysteine protease activity, in the presence of a compound of
10 general formula (I). For example, murine models of *Leishmania* infection, *P. vinckei* infection, malaria (inhibition of falcipain) and *T. cruzi* infection (cruzipain), indicate that inhibition of cysteine proteases that play a key role in pathogen propagation is effective in arresting disease symptoms, 'validating' said targets.

15

The invention therefore extends to the use of a compound of general formula (I) in the validation of a known or putative cysteine protease inhibitor as a therapeutic target.

20. Compounds of general formula (I) are useful for the *in vivo* treatment or prevention of diseases in which participation of a cysteine protease is implicated.

According to a third aspect of the invention, there is provided a compound of general formula (I) for use in medicine, especially for preventing or treating
25 diseases in which the disease pathology may be modified by inhibiting a cysteine protease.

According to a fourth aspect of the invention, there is provided the use of a compound of general formula (I) in the preparation of a medicament for
30 preventing or treating diseases in which the disease pathology may be modified by inhibiting a cysteine protease.

-280-

Certain cysteine proteases function in the normal physiological process of protein degradation in animals, including humans, *e.g.* in the degradation of connective tissue. However, elevated levels of these enzymes in the body can result in pathological conditions leading to disease. Thus, cysteine proteases have been

5 implicated in various disease states, including but not limited to, infections by *Pneumocystis carinii*, *Trypanoma cruzi*, *Trypanoma brucei brucei* and *Crithidia fusiculata*; as well as in osteoporosis, autoimmunity, schistosomiasis, malaria, tumour metastasis, metachromatic leukodystrophy, muscular dystrophy, amyotrophy, and the like. See WO-A-9404172 and EP-A-0603873 and references

10 cited in both of them. Additionally, a secreted bacterial cysteine protease from *S. Aureus* called staphylopain has been implicated as a bacterial virulence factor (Potempa, J., *et al. J. Biol. Chem.*, 262(6), 2664-2667, 1998).

The invention is useful in the prevention and/or treatment of each of the disease

15 states mentioned or implied above. The present invention also is useful in a methods of treatment or prevention of diseases caused by pathological levels of cysteine proteases, particularly cysteine proteases of the papain superfamily, which methods comprise administering to an animal, particularly a mammal, most particularly a human, in need thereof a compound of the present invention. The

20 present invention particularly provides methods for treating diseases in which cysteine proteases are implicated, including infections by *Pneumocystis carinii*, *Trypanoma cruzi*, *Trypanoma brucei*, *Leishmania mexicana*, *Clostridium histolyticum*, *Staphylococcus aureus*, foot-and-mouth disease virus and *Crithidia fusiculata*; as well as in osteoporosis, autoimmunity, schistosomiasis, malaria,

25 tumour metastasis, metachromatic leukodystrophy, muscular dystrophy and amyotrophy.

Inhibitors of cathepsin K, particularly cathepsin K-specific compounds, are useful for the treatment of osteoporosis, Paget's disease, gingival diseases such as

30 gingivitis and periodontitis, hypercalcaemia of malignancy, metabolic bone disease, diseases involving matrix or cartilage degradation, in particular osteoarthritis and rheumatoid arthritis and neoplastic diseases.

-281-

In accordance with this invention, an effective amount of a compound of general formula (I) may be administered to inhibit the protease implicated with a particular condition or disease. Of course, this dosage amount will further be
5 modified according to the type of administration of the compound. For example, to achieve an "effective amount" for acute therapy, parenteral administration of a compound of general formula (I) is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is
10 also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit a cysteine protease. The compounds may be administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of an
15 inventive compound which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect. Prodrugs of compounds of the present invention may be prepared by any suitable method. For those compounds in
20 which the prodrug moiety is a ketone functionality, specifically ketals and/or hemiacetals, the conversion may be effected in accordance with conventional methods.

The compounds of this invention may also be administered orally to the patient, in
25 a manner such that the concentration of drug is sufficient to inhibit bone resorption or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to
30 about 20 mg/kg.

-282-

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention. The compounds of this invention, which may have good bioavailability, may be tested in one of several biological assays to determine the concentration of a compound
5 which is required to have a given pharmacological effect.

According to a fifth aspect of the invention, there is provided a pharmaceutical or veterinary composition comprising one or more compounds of general formula (I) and a pharmaceutically or veterinarily acceptable carrier. Other active materials
10 may also be present, as may be considered appropriate or advisable for the disease or condition being treated or prevented.

The carrier, or, if more than one be present, each of the carriers, must be acceptable in the sense of being compatible with the other ingredients of the
15 formulation and not deleterious to the recipient.

The formulations include those suitable for rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration, but preferably the formulation is an
20 orally administered formulation. The formulations may conveniently be presented in unit dosage form, e.g. tablets and sustained release capsules, and may be prepared by any methods well known in the art of pharmacy.

Such methods include the step of bringing into association the above defined
25 active agent with the carrier. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to methods for preparing a pharmaceutical composition comprising bringing a compound of general formula (I) in
30 conjunction or association with a pharmaceutically or veterinarily acceptable carrier or vehicle.

-283-

Formulations for oral administration in the present invention may be presented as: discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion; or as a bolus etc.

For compositions for oral administration (e.g. tablets and capsules), the term "acceptable carrier" includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, glycerol stearate stearic acid, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring and the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active agent.

Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active agent in an inert base such as gelatin and glycerin,

-284-

or sucrose and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

Parenteral formulations will generally be sterile.

5

According to a sixth aspect of the invention, there is provided a process for the preparation of a pharmaceutical or veterinary composition as described above, the process comprising bringing the active compound(s) into association with the carrier, for example by admixture.

10

Preferred features for each aspect of the invention are as for each other aspect *mutatis mutandis*.

15

Experimental Procedures

Solution Phase Chemistry – General Methods

20

All solvents were purchased from ROMIL Ltd (Waterbeach, Cambridge, UK) at SpS or Hi-Dry grade unless otherwise stated. General peptide synthesis reagents were obtained from Chem-Impex Intl. Inc. (Wood Dale IL 60191. USA). Thin layer chromatography (TLC) was performed on pre-coated plates (Merck aluminium sheets silica 60 F254, part no. 5554). Visualisation of compounds was achieved under ultraviolet light (254nm) or by using an appropriate staining reagent. Flash column purification was performed on silica gel 60 (Merck 9385) or Isolute Flash silica cartridge. All analytical HPLC were obtained on Phenomenex Jupiter C₄, 5 μ , 300A, 250 x 4.6mm, using mixtures of solvent A = 0.1%aq trifluoroacetic acid (TFA) and solvent B = 90% acetonitrile / 10% solvent A on automated Agilent systems with 215 and / or 254nm UV detection. Unless otherwise stated a gradient of 10 – 90% B in A over 25 minutes at 1.5mL / min was performed for full analytical HPLC analysis. HPLC-MS analysis was performed on an Agilent 1100 series LC/MSD, using automated Agilent HPLC

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-285-

systems, with a gradient of 10 – 90% B in A over 10 minutes on Phenomenex Columbus C₈, 5 μ , 300A, 50 x 2.0mm at 0.4mL / min. Nuclear magnetic resonance (NMR) were obtained on a Bruker DPX400 (400MHz 1H frequency; QXI probe) or Bruker DPX500 (500MHz 1H frequency) in the solvents and temperature indicated (298K unless otherwise stated). Chemical shifts are expressed in parts per million (δ) and are referenced to residual signals of the solvent. Coupling constants (*J*) are expressed in Hz. High resolution mass spectrometry was performed on a Micromass QTOF 1.

10 Solid Phase Chemistry – General Methods

Example inhibitors were prepared through a combination of solution and solid phase Fmoc-based chemistries (see 'Solid Phase Peptide Synthesis', Atherton, E. and Sheppard, R. C., IRL Press Ltd, Oxford, UK, 1989, for a general description).

15 An appropriately protected and functionalised building block was prepared in solution (e.g. general compound (6), Scheme 6), then reversibly attached to the solid phase through an appropriate linker followed by rounds of coupling / deprotection / chemical modification (Scheme 6). Example inhibitors were then released (cleaved) from the solid phase, analysed, purified and assayed for inhibition verses a range of proteases.

20 Generally, multipins (polyamide 1.3 \rightarrow 10 μ mole loadings, see www.mimotopes.com) were used for the solid phase synthesis, although any suitable solid phase surface could be chosen. In general, the 1.3 μ mole gears were used to provide small scale crude examples for preliminary screening, whilst the 10 μ mole crowns were used for scale-up synthesis and purification of preferred examples. Standard coupling and Fmoc deprotection methods were employed (see Grabowska, U. *et al*, *J. Comb. Chem.* 2(5), 475-490, 2000. for a thorough description of solid phase multipin methodologies).

30 Preparation of Initial Assembly

-286-

Building Block-linker constructs (e.g. (27), typically 10mg to 100mg) were carboxyl activated with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro phosphate (HBTU, 1 mole equivalent), 1-hydroxybenzotriazole.hydrate (HOBT, 1 mole equivalent) and N-methylmorpholine (NMM, 2 mole equivalents) in dimethylformamide (DMF, typically 1 to 10mL) for 5 minutes. Amino functionalised DA/MDA crowns or HEMA gears (10µmole per crown / 1.2µmole per gear, 0.33 mole equivalent of total surface amino functionalisation compared to activated construct) were added, followed by additional DMF to cover the solid phase surface. The loading reaction was left overnight. Following overnight loading, crowns / gears were taken through standard cycles washing, Fmoc deprotection and loading quantification (see Grabowska, U. *et al*) to provide loaded Building Block-linker constructs (e.g.(28)).

15 Coupling Cycles

The coupling of standard Fmoc-aminoacids (10 or 20 mole equivalent) were performed via carboxyl activated with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro phosphate (HBTU, 10 or 20mole equivalent), 1-hydroxybenzotriazole.hydrate (HOBT, 10 or 20mole equivalent) and N-methylmorpholine (NMM, 20 or 40mole equivalents) in dimethylformamide, with pre-activation for 5 minutes. Activated species were dispensed to the appropriate wells of a polypropylene 96-well plate (Beckman, 1mL wells, 500µL solution per well for crowns or 250µL solution per well for gears) in a pattern required for synthesis. Loaded free amino Building Block-linker constructs (e.g.(28)) were added and the coupling reaction left overnight. Following overnight coupling, crowns / gears were taken through standard cycles washing and Fmoc deprotection (see Grabowska, U. *et al*). Identical activation and coupling conditions were used for the coupling of a range of carboxylic acids (R-COOH). Alternatively, chloroformates e.g. morpholine-4-carbonylchloride (10mole equivalent), were coupled in DMF with the addition of NMM (10mole equivalents).

-287-

Acidolytic Cleavage Cycle

A mixture of 95% TFA / 5% water was pre-dispensed into two polystyrene 96-well plates (Beckman, 1mL wells, 600µL solution per well for crowns or 300µL solution per well for gears) in a pattern corresponding to that of the synthesis. The completed multipin assembly was added to the first plate (mother plate), the block covered in tin foil and cleaved for 2 hours. The cleaved multipin assembly was then removed from the first plate and added to the second plate (washing plate) for 15 minutes. The spent multipin assembly was then discarded and the mother / washing plates evaporated on an HT-4 GeneVac plate evaporator.

Analysis and Purification of Cleaved Examples

- (a) Ex 1.2µmole Gears. 100µL dimethylsulphoxide (DMSO) was added to each post cleaved and dried washing plate well, thoroughly mixed, transferred to the corresponding post cleaved and dried mother plate well and again thoroughly mixed. 10µL of this DMSO solution was diluted to 100µL with a 90% acetonitrile / 10% 0.1%aq TFA mixture. 20µL aliquots were analysed by HPLC-MS and full analytical HPLC. In each case the crude example molecules gave the expected $[M + H]^+$ ion and an HPLC peak at > 80% (by 215nm UV analysis). This provided an approximately 10mM DMSO stock solution of good quality crude examples for preliminary protease inhibitory screening.
- (b) Ex 10µmole Crowns. 500µL of a 90% acetonitrile / 10% 0.1%aq TFA mixture was added to each washing plate well, thoroughly mixed, transferred to the corresponding mother plate well and again thoroughly mixed. 5µL of this solution was diluted to 100µL with a 90% acetonitrile / 10% 0.1%aq TFA mixture. 20µL aliquots were analysed by HPLC-MS and full analytical HPLC. In each case the crude example molecules gave the expected $[M + H]^+$ ion and an HPLC peak at > 80% (by 215nm UV analysis). The polystyrene blocks containing crude examples were then lyophilised.

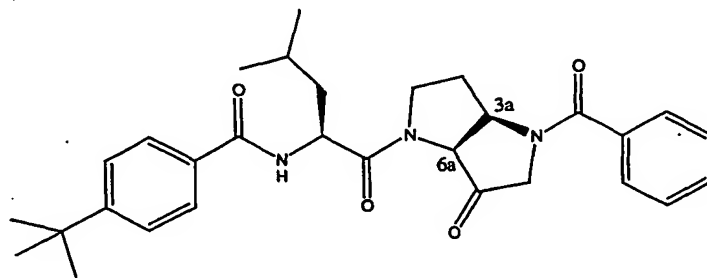
-288-

(c) Individual examples (ex (b)) were re-dissolved in a 1 : 1 mixture of 0.1% aq TFA / acetonitrile (1mL) and purified by semi-preparative HPLC (Phenomenex Jupiter C₄, 5 μ , 300A, 250 x 10mm, a 25-90% B in A gradient over 25mins, 4.0mL/min, 215nm UV detection). Fractions were lyophilised into pre-tarred glass sample vials to provide purified examples (typically 2 to 4mg, 40 to 80% yield).

(d) Purified examples were dissolved in an appropriate volume of DMSO to provide a 10mM stock solution, for accurate protease inhibitory screening.

EXAMPLES 1 – 248 were prepared using the general solid phase descriptions above and are inhibitors of cathepsin K with K_i ranging from 1-5000nM;

EXAMPLE 1. (3*aR*, 6*aS*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-*tert*-butylbenzamide



Following the general details from Scheme 1, the required bicycle building block (3*aS*,6*aR*) 3-Oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9H-fluoren-9-ylmethyl) ester (**6**) was prepared in 8 steps as follows;

(1) Preparation of (2*S*,3*S*) 3-hydroxypyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl) ester.

Trans-3-hydroxy-L-proline (10.0g, 76.3mmole) was added to a vigorously stirred, ice-cooled solution of sodium carbonate (16.90g, 160.2mmole) in water (100mL). 1,4-Dioxan (75mL) was added providing an opaque but

-289-

mobile mixture. 9-Fluorenylmethyl chloroformate (20.31g, 80mmole) in 1,4-dioxan (75mL) was added over 1hr, then the ice-cooling removed and the mixture stirred at RT for an additional 2hr. Additional water (300mL) was added, the reaction mixture washed with chloroform (2 x 250mL) and the combined organic layers discarded. The aqueous phase was acidified with 1N HCl to ~ pH 2, providing a thick opaque mixture. The acidified aqueous mixture was extracted with chloroform (2 x 500mL) and the now clear aqueous phase discarded. The opaque combined chloroform layers were dried (Na₂SO₄), filtered and reduced in vacuo to provide batch 1 (5.70g). The residual precipitate (a mixture of product and drying agent) was triturated with hot methanol (2 x 250mL) and the combined methanol solutions reduced in vacuo to provide batch 2 (10.25g). Batch 1 and 2 were individually analysed by TLC (single UV spot, R_f = 0.15, 20% MeOH in CHCl₃), and HPLC-MS (single main UV peak with R_t = 7.069mins, 354.2 [M + H]⁺, 376.2 [M + Na]⁺) and found to be identical, giving a combined yield of 15.95g (45.2mmole, 59.2%). Analysis by ¹H and ¹³C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

δ_H (DMSO-d₆ at 298K); 1.80-2.02 (2H_γ, m), 3.49-3.62 (2H_δ, m), 4.12-4.38 (H_α, H_β, Fmoc H-9 and CH₂, m), 5.55/5.62 (OH), 7.30-7.31 (2H aromatic, Fmoc H-2 and H-7), 7.35-7.37 (2H aromatic, Fmoc H-3 and H-6), 7.43-7.45 (2H aromatic, Fmoc H-1 and H-8), 7.63-7.65 (2H aromatic, Fmoc H-4 and H-5), 12.8-13.0 (COOH); δ_C (DMSO-d₆ at 298K); 31.70/32.70 (d, C_γ), 44.68/45.32 (d, C_δ), 46.94/46.97 (u, Fmoc C-9), 67.04/67.33 (d, Fmoc CH₂), 68.24/68.51 (u, C_α), 73.12/74.23 (u, C_β), 120.49/120.52 (u, Fmoc C-4 and C-5), 125.49/125.58 (u, Fmoc C-1 and C-8), 127.50 (u, Fmoc C-2 and C-7), 128.04 (u, Fmoc C-3 and C-6), 140.99/141.09 (q, Fmoc C-4' and C-5'), 144.02/144.16 (q, Fmoc C-1' and C-8'), 154.33/154.54 (q, OCON), 172.10/172.39 (COOH).

-290-

(2) Preparation of (2*S*,3*R*) 3-hydroxypyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9H-fluoren-9-ylmethyl) ester.

(2*S*,3*S*) (3-hydroxy)pyrrolidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl) ester (10.9g, 30.8mmole) was dissolved in toluene (75mL) in a Dean-Stark apparatus. Allyl alcohol (20mL) was added followed by *p*-toluenesulphonic acid.hydrate (6.05g, 31.4mmole). The mixture was refluxed for 1hr, cooled and CHCl₃ (300mL) added. The organic layer was washed with NaHCO₃ (300mL), 0.1N HCl (300mL) and brine (300mL), then dried (Na₂SO₄). Filtration and reduction in vacuo gave a pale yellow foam (13.5g). The crude foam was purified over silica gel (150g) eluting with a gradient of heptane : ethyl acetate 3:1 → 1:1. Desired fractions were combined and reduced in vacuo to a colourless gum yield 10.34g (26.3mmole, 85.4%). TLC (single UV spot, R_f = 0.30, heptane : ethyl acetate 1:1), analytical HPLC R_t = 18.849mins, HPLC-MS (single main UV peak with R_t = 8.354mins, 394.2 [M + H]⁺, 416.2 [M + Na]⁺). Analysis by ¹H and ¹³C NMR showed the presence of cis and trans geometrical isomers around the 3° amide bond.

^δ_H (CDCl₃ at 298K); 2.00-2.21 (2H_γ, m), 2.70/2.85 (OH, b), 3.72-3.81 (2H_δ, m), 4.12-4.67 (H_α, H_β, Fmoc H-9 and CH₂, 2 x COOCH₂CH=CH₂, m), 5.20-5.40 (2 x COOCH₂CH=CH₂, m), 5.82-5.99 (1 x COOCH₂CH=CH₂, m), 7.28-7.33 (2H aromatic, Fmoc H-2 and H-7), 7.34-7.41 (2H aromatic, Fmoc H-3 and H-6), 7.53-7.66 (2H aromatic, Fmoc H-1 and H-8), 7.77-7.81 (2H aromatic, Fmoc H-4 and H-5); ^δ_C (CDCl₃ at 298K); 32.28/33.04 (d, C_γ), 44.98/45.32 (d, C_δ), 47.56/47.63 (u, Fmoc C-9), 66.44 (d, COOCH₂CH=CH₂), 68.01/68.11 (d, Fmoc CH₂), 68.32/68.72 (u, C_α), 74.49/75.67 (u, C_β), 119.20/119.48 (d, COOCH₂CH=CH₂), 120.34/120.37 (u, Fmoc C-4 and C-5), 125.36/125.60 (u, Fmoc C-1 and C-8), 127.47 (u, Fmoc C-2 and C-7), 128.06/128.12 (u, Fmoc C-3 and C-6), 131.79/131.94 (u, COOCH₂CH=CH₂), 141.65/141.71 (q, Fmoc C-4' and

-291-

C-5'), 144.12/144.34 (q, Fmoc C-1' and C-8'), 155.13/155.59 (q, OCON), 170.53/170.55 (COOCH₂CH=CH₂).

- (3) Preparation of (2*S*,3*R*) 3-azidopyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9*H*-fluoren-9-ylmethyl) ester.

Diethyl azodicarboxylate (1.24 ml, 7.9 mmol) was added dropwise over 20 minutes to a stirred solution of triphenylphosphine (2.07 g, 7.9 mmol) in tetrahydrofuran (30 ml) at 0°C. The mixture was stirred for 5 minutes at 0°C then a solution of (2*S*, 3*S*)-3-hydroxypyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9*H*-fluoren-9-ylmethyl) ester (2.59 g, 6.6 mmol) and hydrazoic acid (14.3 ml of 0.7M solution in toluene) in tetrahydrofuran (30 ml) was added dropwise over 35 minutes. The mixture was stirred for 5 minutes at 0°C then at ambient temperature for 14 hours. The solvent was removed *in vacuo* and the residue purified by flash chromatography over silica gel eluting with a gradient of heptane : ethyl acetate 5:1 → 3:1. Appropriate fractions were combined and the solvents removed *in vacuo* to obtain (2*S*, 3*R*) 3-azidopyrrolidine-1,2-dicarboxylic acid allyl ester 1-(9*H*-fluoren-9-ylmethyl) ester as a colourless oil (1.45 g, 53%). TLC (single UV spot, R_f = 0.30, heptane : ethyl acetate 3:1), analytical HPLC main UV peak with R_t = 19.896mins and HPLC-MS 419.2 [M+H]⁺, 441.2 [M+Na]⁺.

δ_H (CDCl₃ at 298K); 2.08-2.25 (2H, H-4, m), 3.52-3.59 (1H, H-5, m), 3.68-3.76 (1H, H-5, m), 4.15 (0.5H, Fmoc-CH₂, t, *J* = 6.6Hz), 4.24 (0.5H, Fmoc-CH₂, t, *J* = 7.1Hz), 4.33-4.38 (2H, H-3 and Fmoc-CH, m), 4.44-4.48 (1.5H, 0.5H-2 and Fmoc-CH, m), 4.51-4.66 (1.5H, 0.5H-2 and CH₂CH=CH₂, m), 4.67-4.70 (1H, CH₂CH=CH₂, m), 5.21-5.40 (2H, CH₂CH=CH₂, m), 5.84-5.98 (1H, CH₂CH=CH₂, m), 7.26-7.32 (2H, aromatic, Fmoc H-2 and H-7), 7.37-7.40 (2H, aromatic, Fmoc H-3 and H-6), 7.51-7.60 (2H, aromatic, Fmoc H-1 and H-8), 7.74-7.77 (2H, aromatic, Fmoc H-4 and H-5); δ_C (CDCl₃ at 298K); 29.14/30.13 (d, C-5),

-292-

44.40/44.72 (d, C-5), 47.12/47.21 (u, Fmoc-CH), 61.02/61.87 (u, C-3),
 61.63/62.07 (u, C-2), 66.17 (d, Fmoc-CH₂), 67.65 (d, CH₂CH=CH₂),
 118.86/119.11 (d, CH₂CH=CH₂), 119.94/124.83/124.95/125.05/
 127.03/127.69 (u, aromatic, Fmoc-CH), 131.384/131.50 (u, CH₂CH=CH₂),
 141.29 (q, aromatic Fmoc quaternary carbon b), 143.49/143.65/143.92 (q,
 aromatic Fmoc quaternary carbon a), 154.07/154.49 (q, Fmoc-CO),
 168.62/168.70 (q, allyl-CO).

(4) Preparation of (2*S*,3*R*) 3-azidopyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester.

Dichloromethane (30 ml) then phenyltrihydrosilane (0.81 ml, 6.6 mmol) were added consecutively to a stirred mixture of tetrakis(triphenylphosphine) palladium(0) (76 mg, 0.066 mmol) and (2*S*, 3*R*)-3-azidopyrrolidine-1,2-dicarboxylic acid allyl ester 1-(9*H*-fluoren-9-ylmethyl) ester (1.38 g, 3.3 mmol) under argon. The mixture was stirred for 30 minutes then diluted with chloroform (200 ml) and washed with 0.01M hydrochloric acid (200 ml). The aqueous layer was extracted with chloroform (100 ml), then the combined chloroform layers were dried (Na₂SO₄) and the solvent removed *in vacuo*. The brown residue was purified by flash chromatography over silica gel eluting with a gradient of heptane : ethyl acetate 3.5:1 → 0:1 followed by methanol : dichloromethane 1 : 4. Appropriate fractions were combined and the solvents removed *in vacuo* to leave (2*S*, 3*R*) 3-azidopyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester as a brown foam (890 mg, 71%). TLC (main UV spot, R_f = 0.20, methanol : chloroform 1:9), analytical HPLC main UV peak with R_t = 16.528mins and HPLC-MS 379.2 [M+H]⁺, 401.1 [M+Na]⁺, 779.3 [2M+Na]⁺.

(5) Preparation of (2*S*,3*R*) 3-aminopyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester.

-293-

Acetic acid was added to a suspension of (2*S*, 3*R*) 3-azidopyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester (3.25 g, 8.6 mmol), palladium on carbon (10%, 320 mg) and ethanol (80 ml) under an atmosphere of argon. The mixture was then stirred under an atmosphere of hydrogen for 3.5 hours then the hydrogen was replaced with argon and the suspension stored at 0°C for 14 hours. A further portion of palladium on carbon (10%, 150 mg) was added then the mixture stirred at ambient temperature for 3 hours under an atmosphere of hydrogen. The catalyst was removed by filtration *in vacuo* through a pad of celite which was washed with acetic acid : water (1:1, 150 ml). The filtrate was concentrated *in vacuo* then toluene (50 ml) was added to the residue and solvents removed *in vacuo*. A further portion of toluene was added (50 ml) and the solvent removed *in vacuo* to leave an oily residue which was triturated with diethyl ether (125 ml) to obtain (2*S*, 3*R*) 3-aminopyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester acetate as a pale brown solid (1.05 g, 30%). Analytical HPLC single UV peak with $R_t = 12.541$ mins and HPLC-MS 353.2 $[M+H]^+$, 705.3 $[2M+Na]^+$.

(6) Preparation of (2*S*,3*R*) 3-*tert*-Butoxycarbonylamino-pyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester

A solution of di-*tert*-butyl dicarbonate (210 mg, 0.96 mmol) in 1,4-dioxan (10 ml) was added to a stirred suspension of (2*S*, 3*R*)-3-aminopyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester (360 mg, 0.87 mmol) and sodium carbonate (195 mg, 1.84 mmol) in water (10 ml) and 1,4-dioxan (10 ml) over 1 hour at 0°C. The reaction mixture was stirred for 16 hours at ambient temperature then the majority of solvents were removed *in vacuo*. The residue was dissolved in dichloromethane (200 ml) and water (100 ml) then acidified to pH ~ 2.5 using 1M hydrochloric acid. The dichloromethane layer was separated then the aqueous layer extracted with dichloromethane. The combined dichloromethane layers were dried

-294-

(Na₂SO₄) and the solvent removed *in vacuo*. The orange-brown residue was purified by flash chromatography over silica gel eluting with a gradient of dichloromethane : methanol 19:1 → 9:1. Appropriate fractions were combined and the solvents removed *in vacuo* to leave (2*S*, 3*R*) 3-*tert*-butoxycarbonylaminopyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester as a light brown solid (235 mg, 60%). TLC (single UV spot, R_f = 0.25, methanol : chloroform 1:9), analytical HPLC single UV peak with R_t = 17.476mins and HPLC-MS 397.2 [M-Bu+2H]⁺, 475.2 [M+Na]⁺, 927.4 [2M+Na]⁺.

δ_H (CDCl₃ at 298K); 1.35 (2H, brs Me₃C), 1.48 (1H, brs Me₃C), 1.75-2.20 (2H, m, H-4), 2.75-3.85 (4H, m, H-5, H-3, Fmoc-CH), 3.85-4.60 (4H, m, Fmoc-CH₂, H-2 and NH), 6.20-6.75 (0.5H, brs, NH), 7.05-7.90 (8H, aromatic); δ_C (d₆-DMSO at 298K); 1.39 and 1.46 (9H total, each s, Me₃C), 1.70-1.85 (1H, m, H-4), 1.70-1.85 (1H, m, H-4), 3.24-3.35 (1H, m, H-5), 3.44-3.54 (1H, m, H-5), 4.02-4.30 (5H, m, H-2, H-3, Fmoc-CH₂ and Fmoc-CH), 6.80 and 7.0 (1H total, each brs, NH), 7.30-7.98 (8H, aromatic)

(7) Preparation of (2*S*,3*R*) 3-*tert*-Butoxycarbonylamino-2-(2-diazo-acetyl)-pyrrolidine-1-carboxylic acid 9*H*-fluoren-9-ylmethyl ester.

A solution of *iso*-butyl chloroformate (68 μ l, 0.52 mmol) in dichloromethane (2 ml) and a solution of 4-methylmorpholine (105 μ l, 0.95 mmol) in dichloromethane (2 ml) were simultaneously added in portions to a stirred suspension of (2*S*, 3*R*)-3-*tert*-butoxycarbonylaminopyrrolidine-1,2-dicarboxylic acid 1-(9*H*-fluoren-9-ylmethyl) ester (215 mg, 0.48mmol) in dichloromethane (5 ml) at -15 °C over 20 minutes under an atmosphere of nitrogen. The solution was stirred for 2 hours then additional solutions of *iso*-butyl chloroformate (15 μ l, 0.115 mmol) in dichloromethane (0.5 ml) and 4-methylmorpholine (26 μ l,

-295-

0.237 mmol) in dichloromethane (0.5 ml) were simultaneously added in one portion. The mixture was stirred for 30 minutes at -15 °C then ethereal diazomethane [~ 15 mmol generated from diazald (4.7 g mmol) addition in diethyl ether (75 ml) to sodium hydroxide (5.25 g) in water (7.5 ml)/ethanol (15 ml) at 65°C] was cautiously added and the resulting yellow solution stirred at room temperature for 16 hrs. Acetic acid (~ 1 ml) was cautiously added (until effervescence had ceased), then the mixture was diluted with diethyl ether (100 ml). The ethereal layer was washed with water (3 x 100 ml), dried (Na_2SO_4) and the solvents removed *in vacuo* to leave an oily residue (250 mg) which was purified by flash chromatography over silica gel eluting with a gradient of heptane : ethyl acetate 2:1 \rightarrow 1:1. Appropriate fractions were combined and the solvents removed *in vacuo* to leave (2*S*, 3*R*) 3-*tert*-butoxycarbonylamino-2-(2-diazoacetyl)pyrrolidine-1-carboxylic acid 9*H*-fluoren-9-ylmethyl ester as a pale yellow solid (91 mg, 40%). TLC (single UV spot, $R_f = 0.4$, heptane : ethyl acetate 1:1), analytical HPLC main UV peak with $R_t = 18.363$ mins and HPLC-MS 449.2 $[\text{M}-\text{N}_2+\text{H}]^+$, 499.2 $[\text{M}+\text{Na}]^+$, 975.5 $[2\text{M}+\text{Na}]^+$.

(8) Cyclisation to (3*aS*,6*aR*) 3-Oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9*H*-fluoren-9-ylmethyl) ester (6)

A solution of (2*S*, 3*R*) 3-*tert*-butoxycarbonylamino-2-(2-diazoacetyl)pyrrolidine-1-carboxylic acid 9*H*-fluoren-9-ylmethyl ester (100 mg, 0.21 mmol) in chloroform (2.5 ml) was added dropwise over 28 minutes to a stirred suspension of rhodium (II) acetate dimer (10 mg) in toluene (2.5 ml) at 75°C under an atmosphere of argon. The mixture was stirred for an additional 30 minutes at this temperature then the solvents removed *in vacuo* to leave an oily residue which was purified by flash chromatography over silica gel eluting with a gradient of hexane : ethyl acetate 3:1 \rightarrow 1:1. Appropriate fractions were combined and the solvents removed *in vacuo* to leave (3*aS*, 6*aR*) 3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9*H*-fluoren-9-

-296-

ylmethyl) ester as a white solid (28 mg, 30%). TLC (two UV spots, major and minor R_f = 0.30 and 0.35 respectively, hexane : ethyl acetate 7:3), analytical HPLC broad group of UV peaks with R_t = 20.043-21.472mins and HPLC-MS 449.2 $[M+H]^+$, 471.2 $[M+Na]^+$, 919.4 $[2M+Na]^+$.

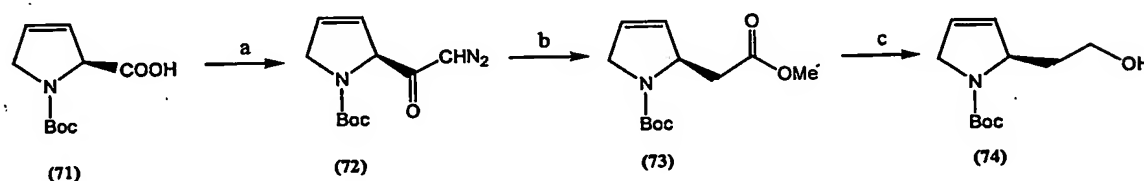
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δ_H ($CDCl_3$ at 298K); (Spectrum poorly resolved) 1.46 (9H, s, Me_3C), 1.85-2.35 (2H, m, H-6), 3.2-5.0 (9H, m, 2 x H-2, H-3a, 2 x H-5, H-6a, Fmoc- $\underline{CH_2}$, Fmoc- \underline{CH}), 7.2-7.85 (8H, aromatic).

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Alternatively, following the general details from Scheme 2, the required bicycle building block (3aS,6aR) 3-Oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9H-fluoren-9ylmethyl) ester (6) was prepared following Schemes 19 and 20;

15



Scheme 19. (a) i. $iBuOCOC$ l, NMM, CH_2Cl_2 , $-15^\circ C$; ii. Ethereal CH_2N_2 , $-15^\circ C$ to RT. (b) MeOH, THF, CF_3CO_2Ag , NMM, $0^\circ C$ to RT in dark. (c) DIBAL-H / THF or $LiBH_4$ / MeOH / THF

20

Preparation of (*S*)-2-(2-diazoacetyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (72)

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2,5-Dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester (71) (1.066 g, 5 mmol) was dissolved with stirring in anhydrous dichloromethane (40 ml). The reaction was flushed with nitrogen and cooled to $-15^\circ C$. *iso*-Butylchloroformate (0.713 ml, 5.5 mmol) in anhydrous dichloromethane (5 ml) and 4-methylmorpholine (1.099 ml, 10 mmol) in anhydrous dichloromethane (5 ml) were added

-297-

simultaneously in 1 ml aliquots over 50 minutes. The mixture was stirred for 2.5 hours at -15°C then ethereal diazomethane [~ 15 mmol generated from addition of diazald (4.7 g) in diethyl ether (75 ml) onto sodium hydroxide (5.25 g) in water (7.5 ml) / ethanol (15 ml) at 60°C] was added to the activated amino acid solution. The mixture was allowed to warm to ambient temperature and stirred for 2.5 hours. A few drops of acetic acid were cautiously added to the mixture, followed by dichloromethane (40 ml). The ethereal layers were washed with aqueous saturated sodium hydrogen carbonate solution (2x 40 ml), dried (Na_2SO_4) and the solvents removed *in vacuo* to leave a yellow residue (1.4 g). Flash chromatography of the residue over silica (35 g) eluting with ethyl acetate : heptane 3 : 7 gave (*S*)-2-(2-diazoacetyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (72) (1.024 g, 86%). TLC (Single spot, $R_f = 0.47$, EtOAc : heptane 1 : 1), analytical HPLC $R_t = 11.537$ min; HPLC-MS 497.2 [$2\text{M} + \text{Na}$] $^{+}$; d_H (500 MHz, CDCl_3) 1.41-1.51 (9H, m, $\text{C}(\text{CH}_3)_3$), 4.11-4.35 (2H, m, BocNCH_2), 4.86-5.05 (1H, m, BocNCH), 5.25-5.50 (1H, m, CHN_2), 5.70-5.80 (1H, m, olefinic CH) and 5.88-6.03 (1H, m, olefinic CH); d_C (125 MHz, CDCl_3) 28.3 and 28.4 ($\text{C}(\text{CH}_3)_3$), 51.8 and 52.3 (CHN_2), 53.65 and 54.0 (BocNCH_2), 71.5 and 72.3 (BocNCH), 80.6 and 80.9 ($\text{OC}(\text{CH}_3)_3$), 126.1 and 126.3 (olefinic CH), 128.35 and 128.5 (olefinic CH), 153.7 and 154.15 (NCO_2), 192.7 and 193.4 (COCHN_2).

Preparation of (*R*)-2-methoxycarbonylmethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (73)

(*S*)-2-(2-Diazoacetyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (72) (912 mg, 3.85 mmol) was dissolved in tetrahydrofuran (14 ml) and methanol (1.6 ml) then cooled to 0°C . A solution of silver trifluoroacetate (94 mg) in 4-methylmorpholine (1.06 ml) was added, and the mixture allowed to warm to ambient temperature over 6 hours in the dark. Methanol (40 ml) was added, followed by 10% aqueous citric acid solution (100 ml). The majority of the organic solvents were removed *in vacuo* then the aqueous phase extracted with ethyl acetate (3x 40 ml). The combined organic layers were washed with brine (40 ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford a residue (1.35 g). Flash

-298-

chromatography of the residue over silica (200 g) eluting with ethyl acetate : hexane 3 : 17 afforded (*R*)-2-methoxycarbonylmethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (73) as a colourless oil (670 mg, 72%). TLC (Single spot, R_f = 0.27, EtOAc : hexane 1 : 4), analytical HPLC R_t = 15.033 min; HPLC-MS 505.3 [2M + Na]⁺; d_H (500 MHz, CDCl₃) 1.44-1.53 (9H, m, C(CH₃)₃), 2.37-2.55 (1H, m, CH₂CO₂Me), 2.90-4.00 (1H, m, CH₂CO₂Me), 3.63-3.70 (3H, m, OCH₃), 3.97-4.26 (2H, m, BocNCH₂), 4.70-4.90 (1H, m, BocNCH), 5.74-5.89 (2H, m, 2x olefinic CH); d_C (125 MHz, CDCl₃) 28.2, 28.3 and 28.5 (C(CH₃)₃), 39.4 and 38.4 (CH₂CO₂Me), 51.5 and 51.6 (OCH₃), 53.3 and 53.5 (BocNCH₂), 60.7 and 60.9 (BocNCH), 79.6 and 80.0 (OC(CH₃)₃), 126.0 and 126.1 (olefinic CH), 129.3 and 129.5 (olefinic CH), 153.9 (NCO₂), 171.5 and 171.7 (CO₂Me).

Preparation of (*R*)-2-(2-hydroxyethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (74)

Diisobutylaluminium hydride (1M solution in tetrahydrofuran, 13.6 ml, 13.6 mmol) was added dropwise over 20 minutes to a stirred solution of (*R*)-2-methoxycarbonylmethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (73) (630 mg, 2.61 mmol) in tetrahydrofuran (20 ml) at -78 °C under a nitrogen atmosphere. The mixture was stirred for 2 hours at -78 °C then at ambient temperature for 18 hours. Methanol (11.94 ml) was slowly added to the mixture, followed by ethyl acetate (40 ml) and magnesium sulfate. The resultant slurry was vigorously stirred for 2 hours, then filtered and the solid residue washed with excess ethyl acetate. The filtrate was evaporated *in vacuo* to afford a residue (1.4 g). Flash chromatography of the residue over silica gel (150 g) eluting with ethyl acetate : hexane 7 : 13 gave (*R*)-2-(2-hydroxyethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (74) (430 mg, 77%). TLC (Single spot, R_f = 0.37, EtOAc : hexane 1 : 1), analytical HPLC R_t = 12.161 min; HPLC-MS 236.1 [M + Na]⁺, 449.3 [2M + Na]⁺; $[a]_D^{22}$ -112° (c=1, CHCl₃); d_H (500 MHz, CDCl₃) 1.42-1.55 (10H, br. s, C(CH₃)₃ and NCHCH₂), 1.84-1.95 (1H, m, NCHCH₂), 3.60-3.72 (2H, m, CH₂OH), 3.93-4.28 (2H, m, BocNCH₂), 4.53-4.78 (1H, m, BocNCH), 5.67-5.84 (2H, m, 2x olefinic CH); d_C (125 MHz, CDCl₃) 28.4 (C(CH₃)₃), 37.4

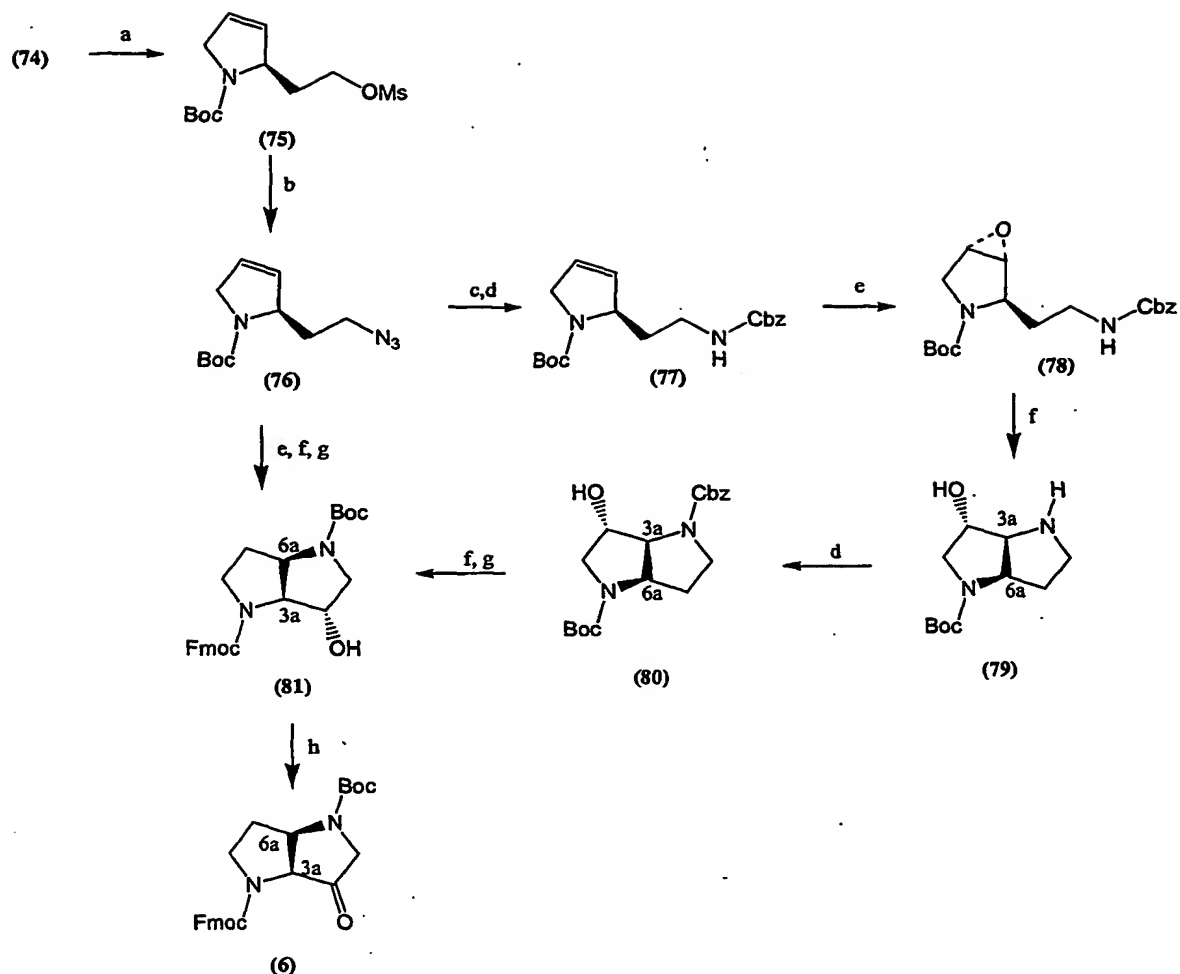
-299-

and 38.7 ($\text{CH}_2\text{CH}_2\text{OH}$), 53.45 and 53.6 (NCH_2), 59.2 and 59.6 (OCH_2), 61.2 and 61.9 (BocNCH), 79.9 and 80.1 ($\text{OC}(\text{CH}_3)_3$), 124.4 and 125.3 (olefinic CH), 130.3 and 131.1 (olefinic CH), 154.4 and 156.0 (NCO_2).

5 Alternative preparation of (R)-2-(2-hydroxyethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (74)

Methanol (0.27 ml, 6.7 mmol) was added dropwise to a stirred suspension of lithium borohydride (146 mg, 6.6 mmol) in tetrahydrofuran (3.5 ml) under an atmosphere of argon over 4 minutes, followed by a solution of (R)-2-methoxycarbonylmethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (73) (0.8 g, 3.3 mmol) in tetrahydrofuran (8 ml) over 15 minutes. The mixture was stirred for 1 hour then poured into water (25 ml). The product was extracted into dichloromethane (3x 20 ml), dried (Na_2SO_4), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 25 : 75 to give (R)-2-(2-hydroxyethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (74) as a colourless oil (0.48 g, 67%), $[\alpha]_D^{22} -127^\circ$ ($c=1$, CHCl_3).

-300-



5 **Scheme 20.** (a) Methanesulfonyl chloride, triethylamine, DCM. (b) Sodium azide, DMF. (c) Ph_3P / H_2O , 1,4-dioxane. (d) 1.05 eq Cbz-Cl, 2.1eq Na_2CO_3 , 1,4-dioxane, water. (e) *m*-Chloroperoxybenzoic acid, DCM. (f) Pd-C / H_2 , ethanol. (g) 1.05 eq Fmoc-Cl, 2.1eq Na_2CO_3 , 1,4-dioxane, water. (h) Dess-Martin periodinane, DCM.

10 **Preparation of (R)-2-(2-methanesulfonyl-ethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (75)**

Triethylamine (2.35 ml, 16.9 mmol) was added dropwise to a stirred solution of (R)-2-(2-hydroxyethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (74) (2.33 g, 10.9 mmol) in dichloromethane (20 ml) at 0 °C over 2 minutes followed

-301-

by methanesulfonyl chloride (1.27 ml, 16.4 mmol) over 4 minutes. The mixture was stirred for 1 hour at 0 °C then washed with water (170 ml) and brine (170 ml), dried (Na₂SO₄) and the solvents removed *in vacuo* to leave a residue (3.42 g), which was used without further purification (see below). HPLC-MS 236.0 [M + 2H - Bu]⁺, 314.1 [M + Na]⁺, 605.1 [2M + Na]⁺.

Preparation of (R)-2-(2-azidoethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (76)

Sodium azide (3.55 g, 54.7 mmol) was added to a stirred solution of (R)-2-(2-methanesulfonylethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (75) (prepared as above) in dimethylformamide (45 ml) under an atmosphere of argon. The mixture was stirred at 60 °C for 1.5 hours then the majority of solvents were removed by distillation *in vacuo* and the residue partitioned between water (200 ml) and ethyl acetate (200 ml). The ethyl acetate layer was washed with brine (150 ml), dried (Na₂SO₄), and the solvents removed *in vacuo* to leave a residue (2.49 g) which was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0: 100 to 10 : 90 to give (R)-2-(2-azidoethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (76) as a colourless oil (2.05 g, 79%). TLC (Single spot, *R_f* = 0.45, EtOAc : hexane 3 : 7), analytical HPLC *R_t* = 15.910 min; HPLC-MS 139.1 [M + 2H - Boc]⁺, 183.1 [M + 2H - Bu]⁺, 499.2 [2M + Na]⁺; *d_H* (500 MHz, CDCl₃) 1.40-1.50 (9H, m, C(CH₃)₃), 1.90-2.10 (2H, m, NCHCH₂), 3.17-3.33 (2H, m, CH₂N₃), 3.96-4.27 (2H, m, BocNCH₂), 4.53-4.68 (1H, m, BocNCH), 5.66-5.86 (2H, m, 2x olefinic CH); *d_C* (125 MHz, CDCl₃) 28.3 and 28.5 (C(CH₃)₃), 32.5 and 33.0 (CH₂CH₂N₃), 47.5 and 47.9 (CH₂N₃), 53.6 and 53.8 (BocNCH₂), 62.0 and 62.3 (BocNCH), 79.55 and 79.9 (OC(CH₃)₃), 125.6 and 126.1 (olefinic CH), 128.9 and 129.4 (olefinic CH), 154.2 and 154.3 (NCO₂), followed by (R)-2-(2-hydroxyethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (74) (22 mg, 9%).

Preparation of (R)-2-(2-benzyloxycarbonylaminoethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (77)

-302-

Water (2.1 ml, 118 mmol) was added to a stirred solution of (*R*)-2-(2-azidoethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (**76**) (2.8 g, 11.8 mmol) and triphenylphosphine (4.6 g, 17.5 mmol) in tetrahydrofuran (350 ml) under an atmosphere of argon. The solution was heated at 45 °C for 7.5 hours then at ambient temperature for 14 hours. An aliquot (18.5 ml, ~0.63 mmol) was removed, concentrated *in vacuo* then azeotroped with toluene (3x 10 ml) and used for the preparation of (2*R*)-2-[2-((2*S*)-2-benzyloxycarbonylamino-4-methylpentanoylamino) ethyl]-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (**140**) (see Scheme 28). An additional 5.0 ml aliquot was removed for analysis, then the remainder of the solution was concentrated *in vacuo* to obtain an oily residue. The residue was dissolved in 1,4-dioxane (35 ml) with stirring, ice-cooled and a solution of sodium carbonate (2.45 g, 23.1 mmol) in water (35 ml) was added. Benzyl chloroformate (2.18 g, 1.824 ml, 12.8 mmol) in 1,4-dioxane (10 ml) was then added dropwise over 30 minutes and the mixture stirred for an additional 30 minutes before adding water (250 ml). The aqueous phase was extracted with dichloromethane (2x 250 ml) and the combined organic layers were dried (Na₂SO₄), filtered and reduced *in vacuo* to leave a clear mobile oil (10.2 g). Flash chromatography over silica, eluting with ethyl acetate : heptane mixtures gave (*R*)-2-(2-benzyloxycarbonylaminoethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (**77**) (3.58 g, 94%) as a mobile colourless oil. TLC (*R*_f = 0.32, EtOAc : heptane 1 : 1), analytical HPLC single main peak, *R*_t = 17.39 min., HPLC-MS 247.1 [M + 2H - Boc]⁺, 291.1 [M + 2H - Bu]⁺, 347.1 [M + H]⁺, 369.1 [M + Na]⁺, 715.2 [2M + Na]⁺; Elemental analysis C₁₉H₂₆N₂O₄ req.(*find.*) % C 65.87 (65.79), % H 7.56 (7.53), % N 8.09 (7.97); HRMS C₁₉H₂₆N₂O₄Na req. 369.1790, *find.* 369.1803 (3.37ppm); δ_H (500 MHz, CDCl₃) 1.45 (9H, br. s, C(CH₃)₃), 1.60-1.95 (2H, m, BocNCHCH₂), 3.00-3.44 (2H, m, CH₂NH), 3.90-4.29 (2H, m, BocNCH₂), 4.45-4.81 (1H, m, BocNCH), 5.01-5.16 (2H, m, OCH₂Ph), 5.50-5.83 (2H, m, 2x olefinic CH) and 7.25-7.38 (6H, m, C₆H₅ and NH); δ_C (125 MHz, CDCl₃) 28.4 (C(CH₃)₃), 34.4, 34.6 (CH₂CH₂NH), 37.2, 37.6 (CH₂NH), 53.6, 53.7 (BocNCH₂), 61.7, 62.1 (BocNCH), 66.4, 66.6 (OCH₂Ph), 79.6, 79.9 (OC(CH₃)₃), 125.2, 125.9, 127.0, 127.6, 127.9, 128.0, 128.4, 129.5,

-303-

130.2 (5x aromatic $\underline{\text{C}}\text{H}$ and 2x olefinic $\underline{\text{C}}\text{H}$), 154.3, 155.0, 156.2, 156.5 ($\text{NH}\underline{\text{C}}\text{O}_2$ and $\text{N}\underline{\text{C}}\text{O}_2$).

**Preparation of (2*R*)-2-(2-benzyloxycarbonylaminoethyl)-6-oxa-3-aza-bicyclo
5 [3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (78)**

(*R*)-2-(2-Benzyloxycarbonylaminoethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (77) (3.57 g, 10.3 mmol) was dissolved in anhydrous dichloromethane (60 ml) with stirring and *meta*-chloroperoxybenzoic acid (27.3 g, 65% reagent, 103 mmol) added. The mixture was stirred at ambient temperature under argon for 16 hours. Dichloromethane (400 ml) was added and the organic phase washed with 10% aqueous w/v solution of sodium hydroxide (2x 400 ml), then dried (Na_2SO_4), filtered and reduced *in vacuo* to leave a clear oil (~5 g). Flash chromatography over silica, eluting with ethyl acetate : heptane mixtures gave (2*R*)-2-(2-benzyloxycarbonyl aminoethyl)-6-oxa-3-aza-bicyclo [3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (78) (3.57 g, 95.3%) as a mobile colourless oil. TLC (R_f = 0.36 (minor) and 0.40 (major) (mixture of *anti* and *syn* epoxides), EtOAc : heptane 2 : 1), analytical HPLC single main peak, R_t = 17.74 min., HPLC-MS 263.1 $[\text{M} + 2\text{H} - \text{Boc}]^+$, 307.1 $[\text{M} + 2\text{H} - \text{Bu}]^+$, 363.1 $[\text{M} + \text{H}]^+$, 20 385.1 $[\text{M} + \text{Na}]^+$, 747.2 $[2\text{M} + \text{Na}]^+$; Elemental analysis $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_5$ req.(*find.*) % C 62.97 (62.93), % H 7.23 (7.22), % N 7.73 (7.61); HRMS $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_5\text{Na}$ req. 385.1739, *find.* 385.1725 (-3.82ppm); d_H (500 MHz, CDCl_3) 1.32-1.62 (10H, m, $\text{C}(\text{CH}_3)_3$ and $\text{CH}_2\text{CH}_2\text{NH}$), 1.67-2.00 (1H, m, $\text{CH}_2\text{CH}_2\text{NH}$), 2.90-4.21 (7H, m, CH_2NH , BocNCHCH , BocNCH_2CH), 4.70-5.17 (2H, m, OCH_2Ph), 5.78-6.05 25 (1H, m, *NH*) and 7.27-7.37 (5H, aromatics); d_C (125 MHz, CDCl_3) 28.1, 28.3, 28.35 and 28.4 ($\text{C}(\underline{\text{C}}\text{H}_3)_3$), 30.8 and 31.2 ($\underline{\text{C}}\text{H}_2\text{CH}_2\text{NH}$), 37.4 and 37.7 ($\underline{\text{C}}\text{H}_2\text{NH}$), 46.15 and 46.6 ($\text{BocN}\underline{\text{C}}\text{H}_2$), 53.9, 54.2, 54.9 and 55.8 (2x epoxide $\underline{\text{C}}\text{H}$), 58.1 and 58.2 ($\text{BocN}\underline{\text{C}}\text{H}$), 66.5 and 66.7 ($\text{O}\underline{\text{C}}\text{H}_2\text{Ph}$), 80.3 and 80.7 ($\text{O}\underline{\text{C}}(\text{CH}_3)_3$), 128.0, 128.1, 128.2, 128.4, 128.5 (5x aromatic $\underline{\text{C}}\text{H}$), 136.7 ($\text{OCH}_2\underline{\text{C}}$), 155.1, 155.9, 156.3 30 and 156.6 ($\text{NH}\underline{\text{C}}\text{O}_2$ and $\text{N}\underline{\text{C}}\text{O}_2$).

-304-

Preparation of (3*S*, 3*aS*, 6*aR*)-3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (79)

(2*R*)-2-(2-Benzoyloxycarbonylaminoethyl)-6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (78) (3.57 g, 9.86 mmol) was dissolved in ethanol (60 ml), cooled to 0 °C and 10% palladium on charcoal (0.40 g) added. The mixture was stirred, then evacuated and flushed with hydrogen. The mixture was allowed to warm to ambient temperature and after 2.5 hours filtered through celite. The filter cake was washed with ethanol (3x 60 ml) and the combined organic filtrates reduced *in vacuo* to provide crude (3*S*, 3*aS*, 6*aR*)-3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (79) (~2.4 g). HPLC-MS 173.1 [M + 2H - Bu]⁺, 229.1 [M + H]⁺.

Preparation of (3*S*, 3*aS*, 6*aR*)-3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 4-benzyl ester 1-*tert*-butyl ester (80)

Crude (3*S*, 3*aS*, 6*aR*)-3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (79) (~2.4 g) was dissolved in 1,4-dioxane (30 ml) with stirring, ice-cooled and a solution of sodium carbonate (2.19 g, 20.7 mmol) in water (25 ml) was added. Benzyl chloroformate (1.63 ml, 11.4 mmol) in 1,4-dioxane (15 ml) was then added dropwise over 30 minutes and the mixture stirred for a further 30 minutes. The mixture was then reduced *in vacuo* by approximately 2/3 volume to leave a mobile pulp. Water (200 ml) was added and the aqueous phase extracted with dichloromethane (2x 100 ml). The combined organic layers were dried (Na₂SO₄), filtered and reduced *in vacuo* to leave a clear mobile oil (3.96 g). Flash chromatography over silica, eluting with ethyl acetate : heptane mixtures gave (3*S*, 3*aS*, 6*aR*)-3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 4-benzyl ester 1-*tert*-butyl ester (80) (2.16 g, 60.5%) as an opaque gum. TLC (*R_f* = 0.15, EtOAc : heptane 1 : 1), analytical HPLC single main peak, *R_t* = 17.15 min., HPLC-MS 263.1 [M + 2H - Boc]⁺, 307.1 [M + 2H - Bu]⁺, 363.1 [M + H]⁺, 385.1 [M + Na]⁺, 747.2 [2M + Na]⁺; Elemental analysis C₁₉H₂₆N₂O₅ req.(*ind.*) % C 62.97 (62.82), % H 7.23 (7.39), % N 7.73 (7.57); HRMS C₁₉H₂₆N₂O₅Na req.

-305-

385.1739, *find.* 385.1725 (2.15ppm); δ_H (400 MHz, CD_3CN , $T = 75^\circ C$) 1.46 (9H, s, $C(CH_3)_3$), 1.90-2.00 (1H, m obscured by NMR solvent peaks, $BocNCHCH_2$), 2.14 (1H, dd, $J = 6.15, 13.15$ Hz, $BocNCHCH_2$), 3.07-3.20 (2H, m, $OH + CbzNCH_2$), 3.24 (1H, dd, $J = 3.8, 12.2$ Hz, $BocNCH_2$), 3.51 (1H, d, $J = 12.2$ Hz, $BocNCH_2$), 3.68 (1H, ddd, $J = 1.7, 8.6, 10.9$ Hz, $CbzNCH_2$), 4.10 (1H, br. d, $J = 5.8$ Hz, $CbzNCH$), 4.27 (1H, br. s, $CHOH$), 4.40-4.46 (1H, m, $BocNCH$), 5.12 (1H, d, $J = 12.7$ Hz, OCH_2Ph), 5.16 (1H, d, $J = 12.7$ Hz, OCH_2Ph) and 7.42-7.29 (5H, aromatics); δ_C (120 MHz, $CDCl_3$) 28.5 ($C(CH_3)_3$), 29.7, 30.4, 31.2, 31.9, 32.0 ($BocNCHCH_2$), 45.5, 45.7 ($CbzNCH_2$), 53.1, 53.4, 53.5 ($BocNCH_2$), 60.1, 61.2 ($BocNCH$), 67.2, 67.6, 68.2, 68.4, 69.0 ($OCH_2Ph + Cbz-NCH$), 72.7, 73.3, 73.4 ($CHOH$), 79.9, 80.1 ($OC(CH_3)_3$), 127.9, 128.0, 128.2, 128.3, 128.5, 128.6, 136.3, 136.4 (aromatics), 154.1, 154.2, 155.2 (2x NCO_2).

Preparation of (3*S*, 3*aS*, 6*aR*)-3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9H-fluoren-9-ylmethyl) ester (81)

(3*S*, 3*aS*, 6*aR*)-3-Hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 4-benzyl ester 1-*tert*-butyl ester (80) (0.54 g, 1.5 mmol) was dissolved in ethanol (10 ml), cooled to $0^\circ C$ and 10% palladium on charcoal (0.055 g) added. The mixture was stirred, then evacuated and flushed with hydrogen. The mixture was warmed to ambient temperature and after 2.5 hours filtered through celite. The filter cake was washed with ethanol (3x 10 ml) and the combined filtrates reduced *in vacuo* to provide the crude amine (~ 0.36 g). HPLC-MS 173.1 $[M + 2H - Bu]^+$, 229.1 $[M + H]^+$. The crude amine was dissolved in 1,4-dioxane (15 ml) with stirring, ice-cooled and a solution of sodium carbonate (0.33 g, 3.15 mmol) in water (15 ml) was added. 9-Fluorenylmethyl chloroformate (0.463 g, 1.79 mmol) in 1,4-dioxane (10 ml) was added dropwise over 30 minutes and the mixture stirred for a further 30 minutes. Water (200 ml) was then added and the aqueous phase extracted with ethyl acetate (2x 100 ml). The combined organic layers were dried (Na_2SO_4), filtered and reduced *in vacuo* to leave a clear mobile oil (1.02 g). Flash chromatography over silica, eluting with ethyl acetate : heptane mixtures gave (3*S*, 3*aS*, 6*aR*)-3-hydroxy hexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic

-306-

acid 1-*tert*-butyl ester 4-(9H-fluoren-9-ylmethyl) ester (**81**) (0.64 g, 95%) as a fine white crystalline solid. TLC (R_f = 0.33, EtOAc : heptane 2 : 1), analytical HPLC single main peak, R_t = 19.98 min., HPLC-MS 395.1 $[M + 2H - Bu]^+$, 451.1 $[M + H]^+$, 473.1 $[M + Na]^+$, 923.2 $[2M + Na]^+$; Elemental analysis $C_{26}H_{30}N_2O_5$ req.(*find.*) % C 69.31 (69.11), % H 6.71 (7.06), % N 6.22 (5.84); HRMS $C_{26}H_{30}N_2O_5Na$ req. 473.2052, *find.* 473.2053 (0.06ppm); δ_H (400 MHz, CD_3CN , $T = 75^\circ C$) 1.46 (9H, s, $C(CH_3)_3$), 1.75-1.90 (1H, m, BocNCHCH₂), 2.05-2.13 (1H, m, BocNCHCH₂), 3.02 (1H, m, FmocNCH₂), 3.08-3.20 (1H, m, BocNCH₂), 3.46 (1H, m, BocNCH₂), 3.46-3.60 (1H, m, FmocNCH₂), 3.90-4.15 (2H, m, FmocNCH and CHOH), 4.28 (1H, t, $J = 6.1$ Hz, FmocCH), 4.34-4.40 (1H, m, BocNCH), 4.49 (2H, d, $J = 6.1$ Hz, FmocCH₂), 7.31-7.45 (4H, m, Fmoc aromatics), 7.65 (2H, d, $J = 7.3$ Hz, Fmoc aromatics), 7.83 (2H, d, $J = 7.5$ Hz, Fmoc aromatics); δ_C (100 MHz, $CDCl_3$) 28.45 ($C(CH_3)_3$), 30.2, 31.2, 32.0 (BocNCHCH₂), 44.8, 45.3, 45.6 (FmocNCH₂), 47.3, 47.4 (FmocCH), 52.8, 53.1, 53.4, 53.5 (BocNCH₂), 60.1, 60.8 (BocNCH), 65.9, 66.2, 67.3 (FmocCH₂), 67.85, 68.4, 68.9 (FmocNCH), 72.5, 72.9, 73.3, 73.6 (CHOH), 79.95 ($OC(CH_3)_3$), 119.8, 120.0, 124.6, 124.9, 125.0, 127.0, 127.4, 127.8 (Fmoc CH aromatics), 141.3, 141.5, 143.7, 143.8, 144.1 (Fmoc quaternary aromatics), 154.0, 154.3, 155.0, 155.2 (2x NCO_2).

Alternative preparation of (3*S*, 3*aS*, 6*aR*)-3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9H-fluoren-9-ylmethyl) ester (81**)**

meta-Chloroperoxybenzoic acid (864 mg, 57-86%) was added to a solution of (*R*)-2-(2-azidoethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (**76**) (175 mg, 0.735 mmol) in anhydrous dichloromethane (4 ml). The mixture was stirred at ambient temperature for 7 hours then saturated aqueous sodium hydrogen carbonate solution (40 ml) and dichloromethane (60 ml) were added. The phases were mixed and separated and the organic phase washed with 10% aqueous sodium hydroxide solution (40 ml), dried (Na_2SO_4) and evaporated *in vacuo* to afford a residue (185 mg). The residue was dissolved in ethanol (6.8 ml) and cooled to $0^\circ C$. 10% Palladium on carbon (84 mg) was added to the mixture and

-307-

the atmosphere purged with hydrogen gas. The mixture was stirred overnight under a hydrogen atmosphere at ambient temperature, filtered over celite and the filter cake washed with excess ethyl acetate. The filtrate was concentrated *in vacuo*, and the residue suspended in a solution of sodium carbonate (193 mg, 1.82 mmol) in water (4 ml). 1,4-Dioxane (2 ml) was added and the mixture cooled to 0 °C, then a solution of 9-fluorenylmethyl chloroformate (198 mg, 0.77 mmol) in 1,4-dioxane (2 ml) added in small portions over 40 minutes. The mixture was then allowed to warm to ambient temperature over 40 minutes. Water (40 ml) was added and the product extracted into dichloromethane (3x 40 ml). The combined organic layers were dried (Na₂SO₄) and evaporated *in vacuo* to afford a residue (335 mg). Flash chromatography of the residue over silica gel (35 g) eluting with ethyl acetate : heptane mixtures 1 : 4 followed by 1 : 1 gave (3*S*, 3*aS*, 6*aR*)-3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9H-fluoren-9-ylmethyl) ester (81) (90 mg, 27%). TLC (Single spot, *R_f* = 0.24, EtOAc : heptane 1 : 1), analytical HPLC *R_t* = 16.348 min; HPLC-MS 451.2 [M + H]⁺, 473.2 [M + Na]⁺, 923.4 [2M + Na]⁺; d_H (500 MHz, CDCl₃) 1.36-1.49 (9H, s, C(CH₃)₃), 1.65-2.25 (3H, m, BocNCHCH₂ and OH), 2.85-3.68 (5H, m, FmocNCH₂, BocNCH₂ and FmocNCH), 4.05-4.80 (5H, m, OCH₂CH, OCH₂, CHOH and BocNCH), 7.26-7.45 (4H, m, Fmoc aromatic CH), 7.53-7.64 (2H, m, Fmoc aromatic CH) and 7.73-7.80 (2H, m, Fmoc aromatic CH);

Preparation of (3*aS*, 6*aR*)-3-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9H-fluoren-9-ylmethyl) ester (6)

(3*S*, 3*aS*, 6*aR*)-3-Hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9H-fluoren-9-ylmethyl) ester (81) (0.495 g, 1.10 mmol) was dissolved in anhydrous dichloromethane (18 ml) with stirring under argon. Dess-Martin periodinane (0.962 g, 2.27 mmol) was added and the mixture stirred for 4 hours. The mixture was concentrated *in vacuo* and the residue purified by flash chromatography over silica, eluting with ethyl acetate : heptane mixtures to give (3*aS*, 6*aR*)-3-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9H-fluoren-9-ylmethyl) ester (6) (0.480 g, 97%) as a white

-308-

crystalline solid. TLC (R_f = 0.38, EtOAc : heptane 1 : 1), analytical HPLC single broad main peak, R_t = 20.27-21.79 min., HPLC-MS 393.1 $[M + 2H - Bu]^+$, 449.1 $[M + H]^+$, 471.1 $[M + Na]^+$, 919.2 $[2M + Na]^+$; Elemental analysis $C_{26}H_{28}N_2O_5 \cdot 0.25EtOAc$ req.(*find.*) % C 68.96 (68.88), % H 6.43 (6.61), % N 5.95 (5.95); HRMS $C_{26}H_{28}N_2O_5Na$ req. 471.1896, *find.* 471.1903 (1.44ppm); δ_c (125 MHz, $CDCl_3$) 28.36 ($C(\underline{CH}_3)_3$), 30.50, 30.93, 31.20 ($BocNCH\underline{CH}_2$), 45.68 ($FmocN\underline{CH}_2$), 47.20 ($Fmoc\underline{CH}$), 51.71, 52.22 ($BocN\underline{CH}_2$), 57.58, 58.64 ($BocN\underline{CH}$), 63.03, 63.57 ($FmocN\underline{CH}$), 67.70, 68.06 ($Fmoc\underline{CH}_2$), 81.10 ($OC(\underline{CH}_3)_3$), 119.94, 124.99, 125.15, 125.29, 127.05, 127.55, 127.71, 127.85 (Fmoc \underline{CH} aromatics), 143.69, 143.92, 144.23 (Fmoc quaternary aromatics), 153.99, 154.74, 155.04 (2x $N\underline{CO}_2$), 206.33, 206.59 ($\underline{C=O}$).

Following the general details from Scheme 6, the required bicycle building block (3a*S*,6a*R*) 3-Oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9*H*-fluoren-9-ylmethyl) ester (6) was converted to building block-linker construct (27) as follows:

A solution of sodium acetate trihydrate (42 mg, 0.311 mmol) in water (0.5 ml) was added to a solution of (3a*S*, 6a*R*) 3-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-(9*H*-fluoren-9-ylmethyl) ester (18.6 mg, 0.0415 mmol) and 4-[(hydrazinocarbonyl)amino]methylcyclohexane carboxylic acid. trifluoroacetate (Murphy, A. M., *et al*, J. Am. Chem. Soc, 114, 3156-3157, 1992) (68 mg, 0.208 mmol) in ethanol (2.0 ml). Remaining traces of sodium acetate were rinsed into the mixture using a further aliquot of ethanol (1.5 ml) then the reaction heated at 75 °C in a sealed tube for 1 hour. The mixture was stood at ambient temperature for 14 hours then heated at 75°C for 2.5 hours. The product was extracted into chloroform (60 ml) then washed with hydrochloric acid (0.1M, 2 x 30 ml), saturated aqueous sodium chloride solution (30 ml) then dried (Na_2SO_4) and the solvent removed *in vacuo* to leave the product as a pale yellow oil (22.9 mg, 86%). Analytical HPLC has main UV peaks with R_t = 19.706 and 21.287mins and HPLC-MS (main UV peaks each with 646.3 $[M+H]^+$).

-309-

Following the general details from Scheme 6, the required building block-linker construct (27) was attached to the solid phase providing loaded building block-linker construct (28) as follows:

5

Building block-linker construct (27) (35.5 μ moles mmoles), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluoro phosphate (HBTU, 13.5mg, 35.5 μ moles mmoles), 1-hydroxybenzotriazole.hydrate and (HOBT, 5.5mg, 35.5 μ moles mmoles) were dissolved in dimethylformamide (1.5mL) and N-methylmorpholine (NMM, 7.8 μ L, 71 μ moles mmoles) added. After pre-activation for 5 minutes, free amine gears (10 x 1.3 μ mole) were added and left overnight. The spent coupling solution was then added to free amine gears (6 x 1.3 μ mole) and left overnight. Standard washing and analyses indicated quantitative loading.

15 Following the general details from Scheme 6, the required loaded building block-linker construct (28) was elaborated on the solid phase as follows:

Loaded construct (28) was elaborated to EXAMPLE 1 (3*aR*, 6*aS*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-*tert*-butylbenzamide by standard Fmoc deprotection and sequential rounds of coupling and washing with the appropriate reagents as follows:-

- 20
- (i) Fmoc-Leu-OH (2 x 20eq, overnight and 4 hr), HBTU, HOBT, NMM activation in DMF
 - 25 (ii) Standard Fmoc deprotection
 - (iii) 4-*tert*-butylbenzoic acid (1 x 10eq, overnight), HBTU, HOBT, NMM activation in DMF
 - (iv) Treatment with 35%TFA in dichloromethane for 30mins, followed by washing with 2 x DMF, 1 x 2%NMM in DMF, 4 x DMF, 4 x
 - 30 acetoneitrile.
 - (v) Benzoic anhydride (20eq) and NMM (5eq) in DMF for 20hr.

-310-

The crude example was cleaved and analysed (see general techniques). HPLC Rt = 18.879-19.62mins (>90%), HPLC-MS 504.3 [M + H]⁺, 1029.5 [2M + Na]⁺.

5 The solid phase experimental detailed for EXAMPLE 1 may be followed to couple with a vast range of aminoacids, carboxylic acids, sulphonyl chlorides etc to provide a vast range of analogues of general formula I.

10 In certain combinations of groupings, the order of solid phase events is amended. For example, when preparing EXAMPLE 194, the U substituent contains an amine group that requires protection via the Boc group, thus the following order of events is utilised :-

- (vi) Fmoc-Leu-OH (2 x 20eq, overnight and 4 hr), HBTU, HOBT, NMM activation in DMF
- 15 (vii) Treatment with 35%TFA in dichloromethane for 30mins, followed by washing with 2 x DMF, 1 x 2%NMM in DMF, 4 x DMF, 4 x acetonitrile.
- (viii) Benzoic anhydride (20eq) and NMM (5eq) in DMF for 20hr.
- (ix) Standard Fmoc deprotection
- 20 (x) 4-(4-Carboxyphenyl)-piperazine-1-carboxylic acid *tert*-butyl ester sodium salt (1 x 10eq, overnight), HBTU, HOBT, NMM activation in DMF.
- (xi) Standard cleavage

25 As a further variation, when preparing EXAMPLE 151, the following order of events is utilised :-

- (xii) Fmoc-Leu-OH (2 x 20eq, overnight and 4 hr), HBTU, HOBT, NMM activation in DMF
- 30 (xiii) Standard Fmoc deprotection
- (xiv) 4-Dimethylaminobenzoic acid (1 x 10eq, overnight), HBTU, HOBT, NMM activation in DMF

-311-

- (xv) Washing with 1 x DMF, 1 x 20% piperidine in DMF, 4 x DMF, 4 x acetonitrile.
- (xvi) Treatment with 35%TFA in dichloromethane for 30mins, followed by washing with 2 x DMF, 1 x 2%NMM in DMF, 4 x DMF, 4 x acetonitrile.
- 5 (xvii) Fmoc-Leu-OH (20eq, overnight), HBTU, HOBT, NMM activation in DMF.
- (xviii) Standard Fmoc deprotection
- (xix) Acetic anhydride (50eq) and NMM (25eq) in DMF for 1hr.
- 10 (xx) Washing with 1 x DMF, 1 x 20% piperidine in DMF, 4 x DMF, 4 x acetonitrile.
- (xxi) Standard cleavage

As a further variation, when preparing EXAMPLE 80, the following order of events is utilised :-

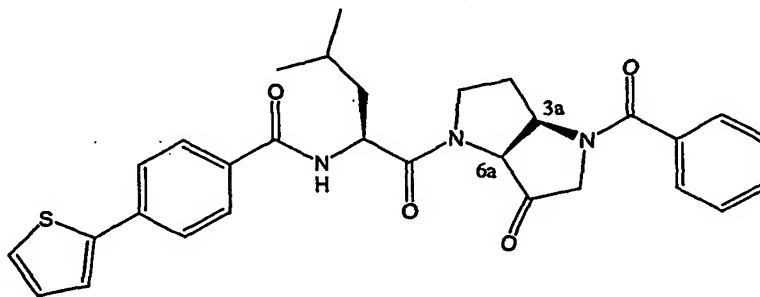
15

- (xxii) Fmoc-Leu-OH (2 x 20eq, overnight and 4 hr), HBTU, HOBT, NMM activation in DMF
- (xxiii) Treatment with 35%TFA in dichloromethane for 30mins, followed by washing with 2 x DMF, 1 x 2%NMM in DMF, 4 x DMF, 4 x acetonitrile.
- 20 (xxiv) Pyridine-2-carboxylic acid (20eq) and NMM (5eq) in DMF for 20hr.
- (xxv) Washing with 2 x DMF, 1 x 2%NMM in DMF, 4 x DMF, 4 x acetonitrile.
- 25 (xxvi) Oxidation with m-chloroperbenzoic acid (5eq) in DCM for 8hrs.
- (xxvii) Washing with 4 x DMF, 4 x acetonitrile.
- (xxviii) Standard Fmoc deprotection
- (xxix) 4-Dimethylaminobenzoic acid (1 x 10eq, overnight), HBTU, HOBT, NMM activation in DMF.
- 30 (xxx) Washing with 1 x DMF, 1 x 20% piperidine in DMF, 4 x DMF, 4 x acetonitrile.
- (xxxi) Standard cleavage

-312-

The following examples (2 – 248) were prepared as detailed for EXAMPLE 1, coupling with the required reagents to provide the full length molecule (see i → v, or vi → xi, or xii → xxi above, or xxii → xxxi above). For step (v), (viii) and (xix) where the anhydride is not readily available, an R²COOH (20eq) / HBTU (20eq) / HOBT (20eq) / NMM (40eq) mixture in DMF with overnight coupling may be used or an RNHCOC₂H₅ (20eq) / NMM (10eq) mixture in DMF with overnight coupling may be used or an RNCO (20eq) mixture in DMF with overnight coupling may be used. Following final coupling where the R² or U groups contain a protonatable nitrogen (e.g. pyridyl or 4-dimethylaminobenzoyl), the solid phase intermediate is treated with 20% piperidine in DMF for 10mins followed by standard washing protocols prior to cleavage.

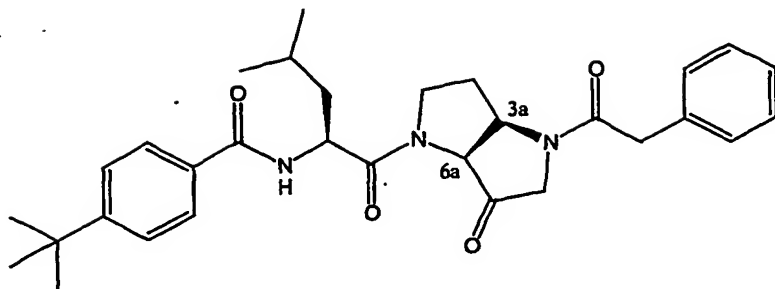
EXAMPLE 2. (3*aR*, 6*aS*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-thiophen-2-yl-benzamide



HPLC Rt = 18.0-19.2 mins (> 90%), HPLC-MS 530.2 [M + H]⁺, 1081.4 [2M + Na]⁺.

EXAMPLE 3. (3*aR*, 6*aS*)-4-*tert*-Butyl-*N*-[(1*S*)-3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-benzamide

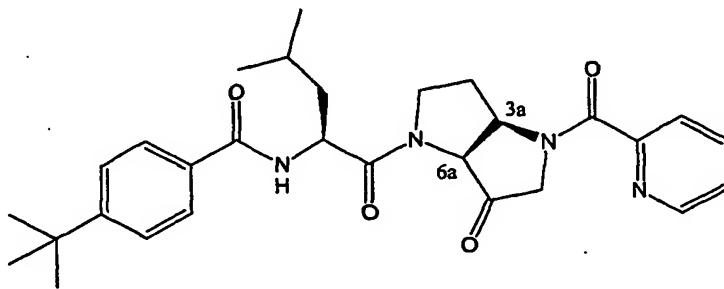
-313-



HPLC Rt = 19.1-20.2 mins (> 90%), HPLC-MS 518.3 [M + H]⁺, 1057.6 [2M + Na]⁺.

5

EXAMPLE 4. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

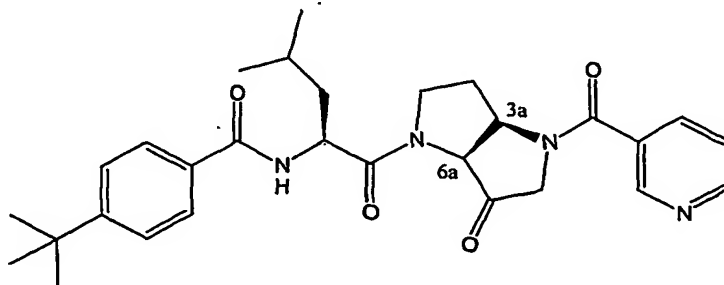


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HPLC Rt = 17.2-18.1 mins (> 90%), HPLC-MS 505.3 [M + H]⁺, 1031.5 [2M + Na]⁺.

EXAMPLE 5. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

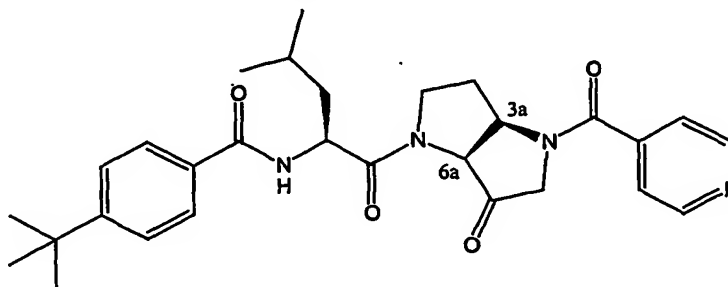
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-314-

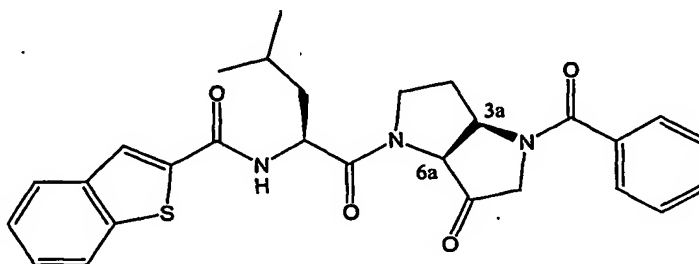
HPLC Rt = 15.2-16.4 mins (> 90%), HPLC-MS 505.3 [M + H]⁺, 1031.5 [2M + Na]⁺.

EXAMPLE 6. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



HPLC Rt = 15.3-16.4 mins (> 90%), HPLC-MS 505.3 [M + H]⁺, 523.3 [M + H + H₂O]⁺.

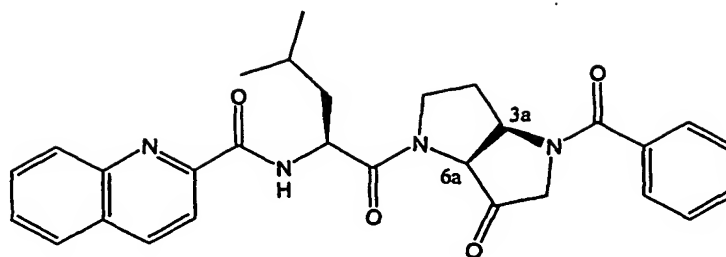
EXAMPLE 7. (3a*R*, 6a*S*)-Benzo[*b*]thiophene-2-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide



HPLC Rt = 16.8-17.9 mins (> 90%), HPLC-MS 504.2 [M + H]⁺.

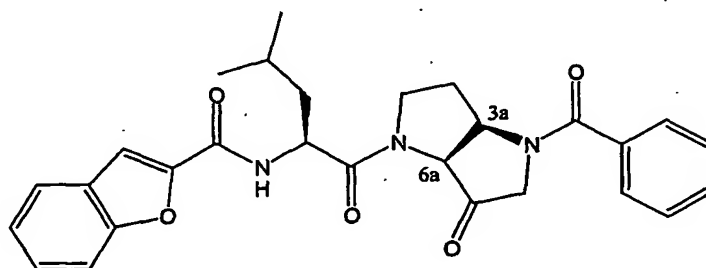
EXAMPLE 8. (3a*R*, 6a*S*)-Quinoline-2-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide

-315-



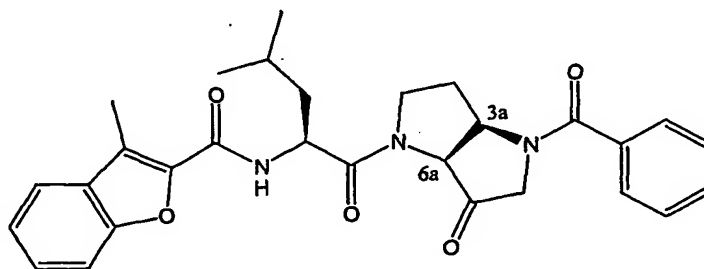
HPLC R_t = 17.0-17.8 mins (> 90%), HPLC-MS 499.1 $[M + H]^+$.

- 5 **EXAMPLE 9.** (3a*R*, 6a*S*)-Benzofuran-2-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide



- 10 HPLC R_t = 16.2-17.7 mins (> 90%), HPLC-MS 488.1 $[M + H]^+$, 997.2 $[2M + Na]^+$.

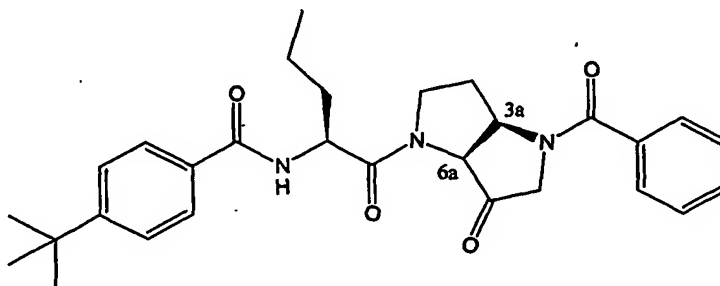
- EXAMPLE 10.** (3a*R*, 6a*S*)-3-Methyl-benzofuran-2-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide
- 15



-316-

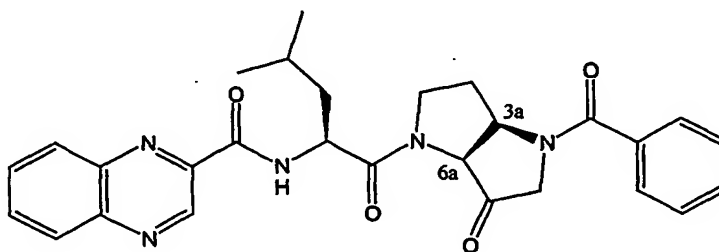
HPLC Rt = 17.8-18.9 mins (> 85%), HPLC-MS 502.1 [M + H]⁺, 520.1 [M + H + H₂O]⁺.

5 EXAMPLE 11. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-4-*tert*-butyl-benzamide



10 HPLC Rt = 17.4-18.2 mins (> 90%), HPLC-MS 490.2 [M + H]⁺.

EXAMPLE 12. (3a*R*, 6a*S*)-Quinoxaline-2-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide

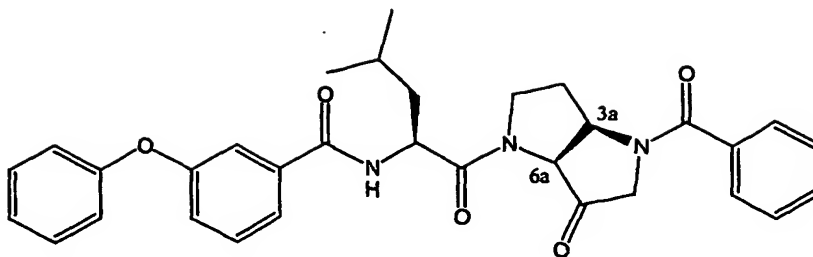


15 HPLC Rt = 15.6-16.7 mins (> 90%), HPLC-MS 500.2 [M + H]⁺.

EXAMPLE 13. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-3-phenoxy-benzamide

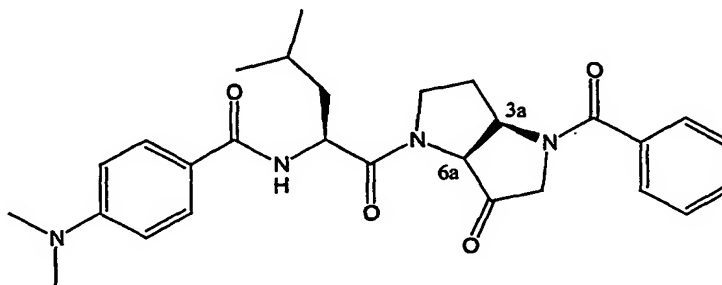
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-317-



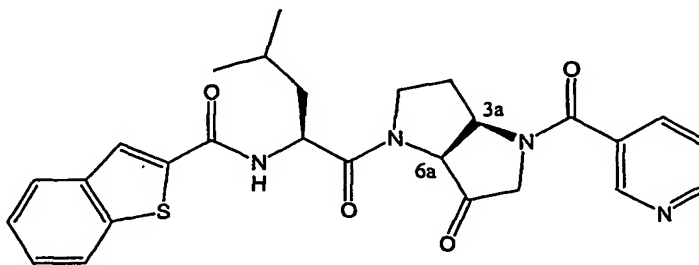
HPLC Rt = 18.5-19.7 mins (> 80%), HPLC-MS 540.1 [M + H]⁺.

- 5 **EXAMPLE 14.** (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-dimethylamino-benzamide



- 10 HPLC Rt = 12.16 mins (> 90%), HPLC-MS 491.2 [M + H]⁺, 509.2 [M + H + H₂O]⁺.

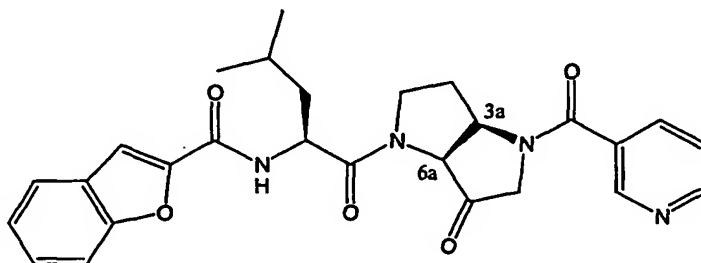
- EXAMPLE 15.** (3a*R*, 6a*S*)-Benzo[*b*]thiophene-2-carboxylic acid {(1*S*)-3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide
- 15



-318-

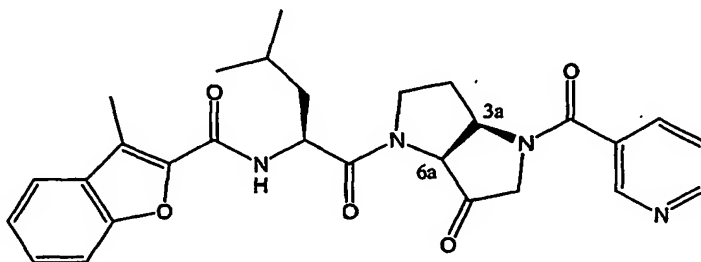
HPLC Rt = 13.93 mins (> 95%), HPLC-MS 505.2 [M + H]⁺.

EXAMPLE 16. (3a*R*, 6a*S*)-Benzofuran-2-carboxylic acid {(1*S*)-3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide



HPLC Rt = 13.42 mins (> 85%), HPLC-MS 489.2 [M + H]⁺, 999.4 [2M + Na]⁺.

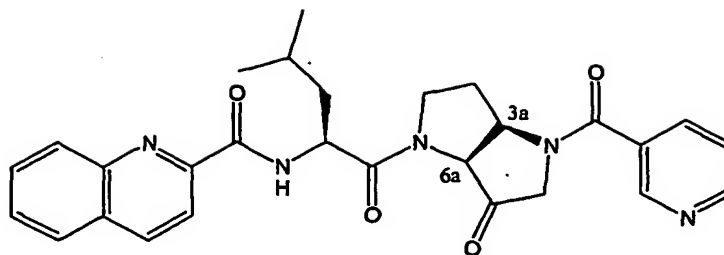
EXAMPLE 17. (3a*R*, 6a*S*)-3-Methyl-benzofuran-2-carboxylic acid {(1*S*)-3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide



HPLC Rt = 14.58 mins (> 90%), HPLC-MS 503.2 [M + H]⁺.

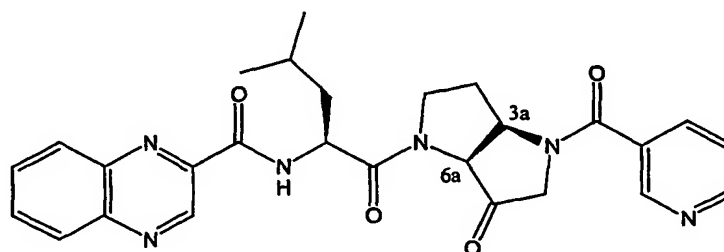
EXAMPLE 18. (3a*R*, 6a*S*)-Quinoline-2-carboxylic acid {(1*S*)-3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-amide

-319-



HPLC Rt = 14.00 mins (> 90%), HPLC-MS 500.2 [M + H]⁺.

- 5 EXAMPLE 19. (3aR, 6aS)-Quinoxaline-2-carboxylic acid {(1S)-3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl}-amide

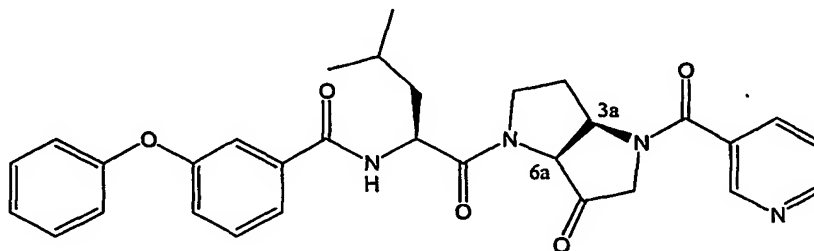


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HPLC Rt = 12.77 mins (> 90%), HPLC-MS 501.2 [M + H]⁺.

- EXAMPLE 20. (3aR, 6aS)-N-[(1S)-3-Methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl]-3-phenoxy-benzamide

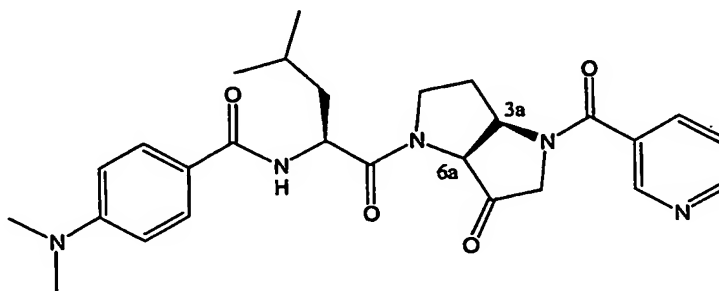
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HPLC Rt = 16.06 mins (> 85%), HPLC-MS 541.2 [M + H]⁺.

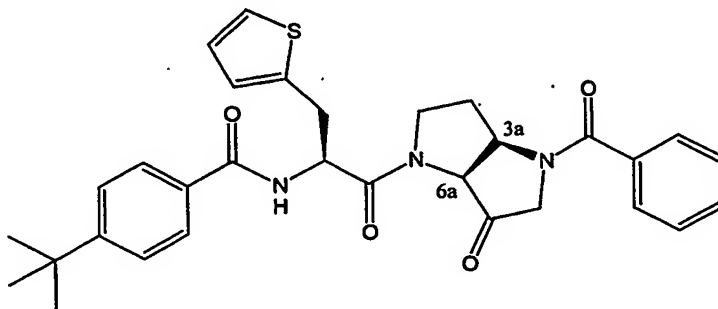
-320-

EXAMPLE 21. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



HPLC R_t = 8.70 mins (> 95%), HPLC-MS 255.6 $[M + 2H + H_2O]^{2+}$, 492.2 $[M + H]^+$, 510.2 $[M + H + H_2O]^+$.

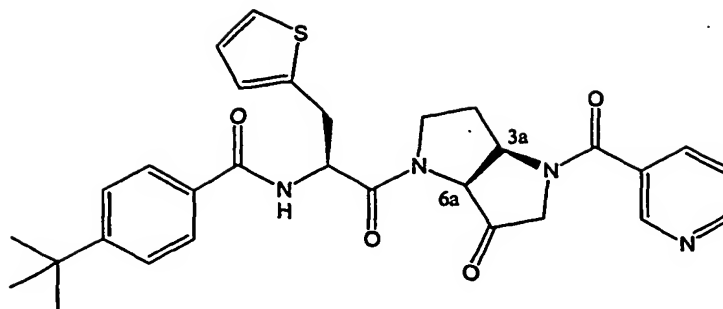
EXAMPLE 22. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-2-oxo-1-thiophen-2-ylmethyl-ethyl]-4-*tert*-butyl-benzamide



HPLC R_t = 18.0-19.0 mins (> 80%), HPLC-MS 544.2 $[M + H]^+$.

EXAMPLE 23. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-2-oxo-2-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-thiophen-2-ylmethyl-ethyl}-benzamide

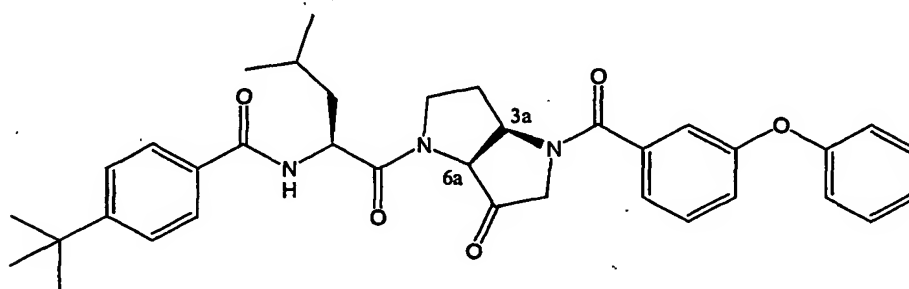
-321-



HPLC Rt = 15.626 mins (> 85%), HPLC-MS 545.2 [M + H]⁺.

5

EXAMPLE 24. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(3-phenoxy-benzoyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

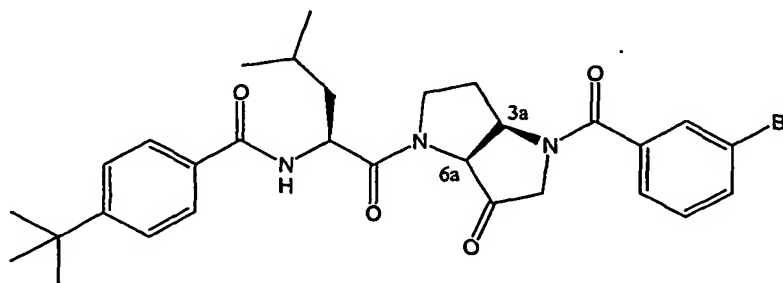


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HPLC Rt = 22.0-23.2 mins (> 75%), HPLC-MS 596.1 [M + H]⁺.

EXAMPLE 25. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(3-Bromo-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide

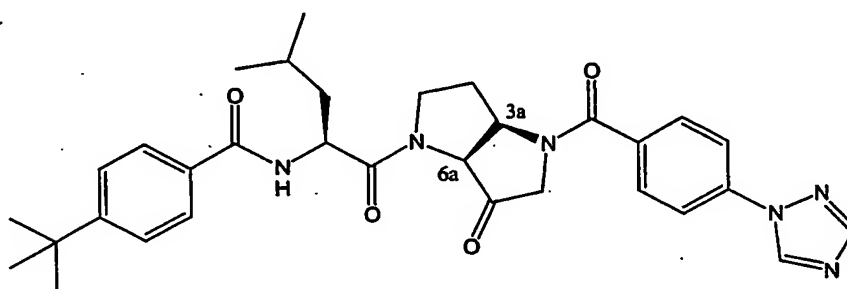
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-322-

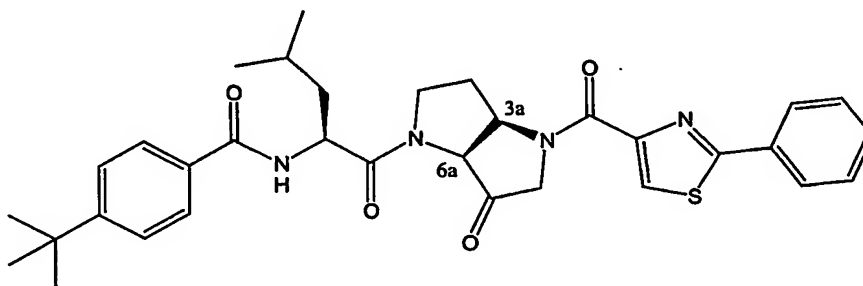
HPLC Rt = 20.3-21.5 mins (> 80%), HPLC-MS 582.1 / 584.1 [M + H]⁺.

EXAMPLE 26. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(4-[1,2,4]triazol-1-yl-benzoyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



HPLC Rt = 17.4-18.7 mins (> 80%), HPLC-MS 571.1 [M + H]⁺.

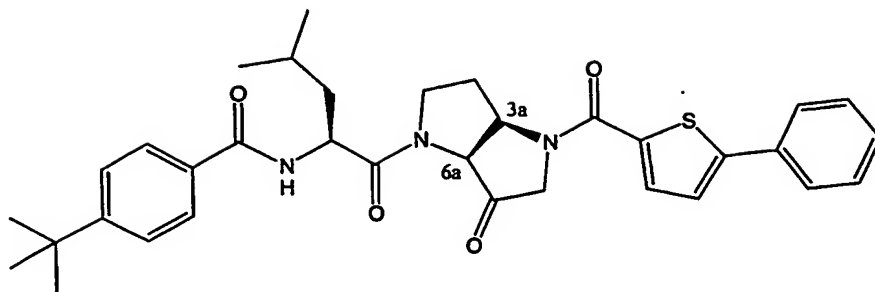
EXAMPLE 27. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(2-phenylthiazole-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



HPLC Rt = 21.4-22.7 mins (> 80%), HPLC-MS 587.1 [M + H]⁺.

EXAMPLE 28. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(5-phenylthiophene-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

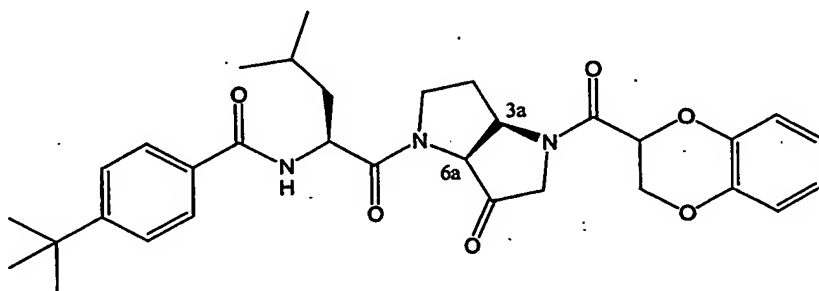
-323-



HPLC Rt = 22.0-23.0 mins (> 70%), HPLC-MS 586.1 [M + H]⁺.

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EXAMPLE 29. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-1-[4-(2,3-dihydrobenzo[1,4]dioxine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

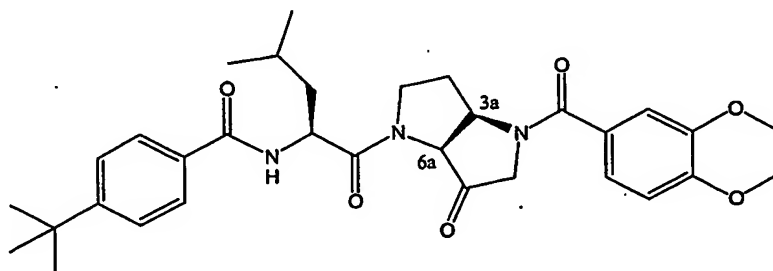


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HPLC Rt = 20.1-21.3 mins (> 80%), HPLC-MS 562.1 [M + H]⁺.

EXAMPLE 30. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-1-[4-(2,3-dihydrobenzo[1,4]dioxine-6-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

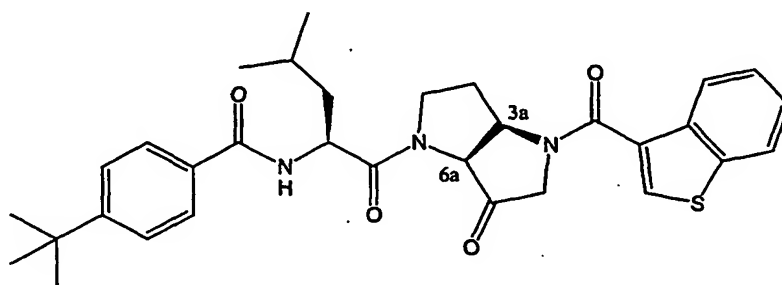
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-324-

HPLC Rt = 18.3-19.1 mins (> 85%), HPLC-MS 562.1 [M + H]⁺.

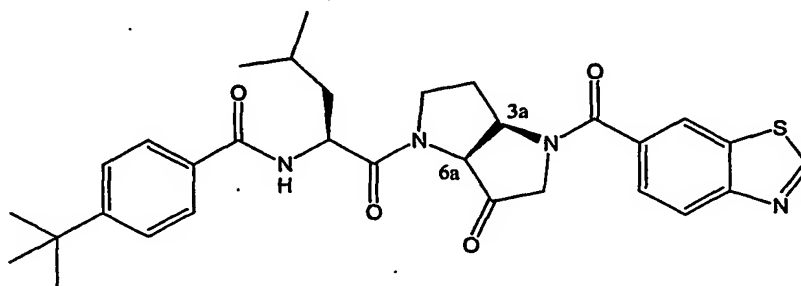
5 EXAMPLE 31. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(Benzo[*b*]thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide



10 HPLC Rt = 20.5-21.8 mins (> 80%), HPLC-MS 560.2 [M + H]⁺.

EXAMPLE 32. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(Benzothiazole-6-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide

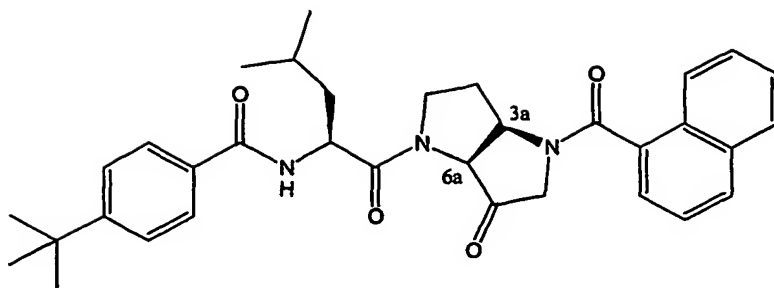
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HPLC Rt = 17.9-18.9 mins (> 75%), HPLC-MS 561.2 [M + H]⁺.

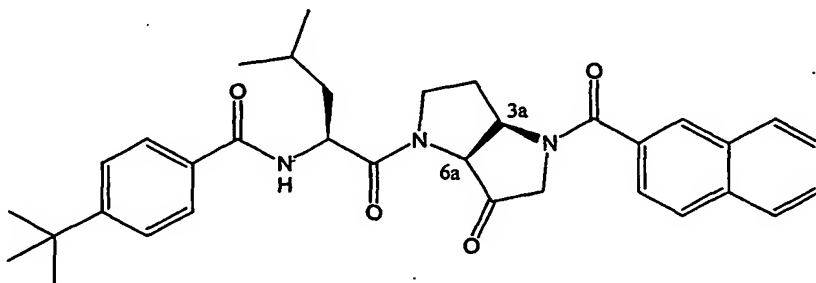
20 EXAMPLE 33. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-3-methyl-1-[4-(naphthalene-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

-325-



HPLC Rt = 20.5-21.7 mins (> 80%), HPLC-MS 554.1 [M + H]⁺.

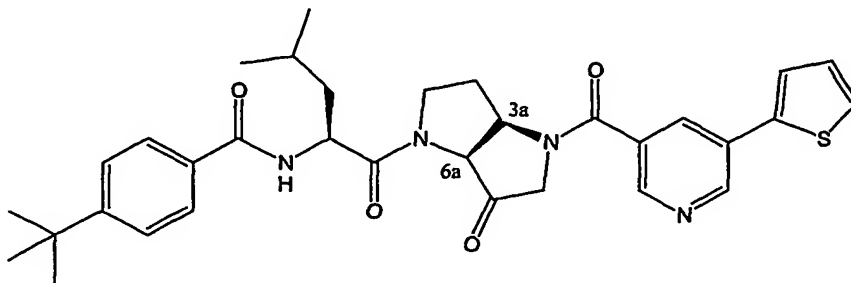
- 5 EXAMPLE 34. (3aR, 6aS)-4-*tert*-Butyl-*N*-{(1*S*)-3-méthyl-1-[4-(naphthalene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



- 10 HPLC Rt = 20.7-21.8 mins (> 75%), HPLC-MS 554.2 [M + H]⁺.

EXAMPLE 35. (3aR, 6aS)-4-*tert*-Butyl-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(5-thiophen-2-yl-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

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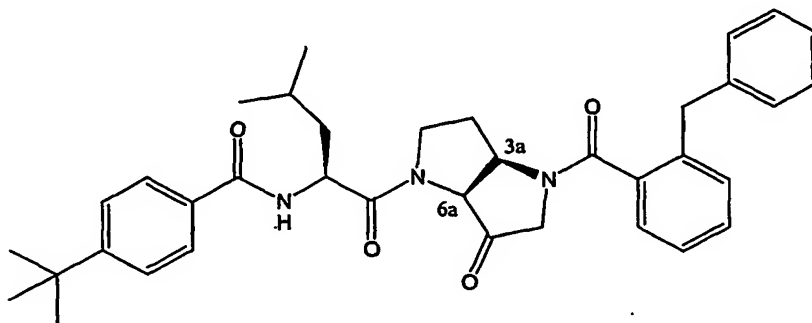


-326-

HPLC Rt = 18.9-19.8 mins (> 70%), HPLC-MS 587.1 [M + H]⁺.

EXAMPLE 36. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(2-Benzyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide

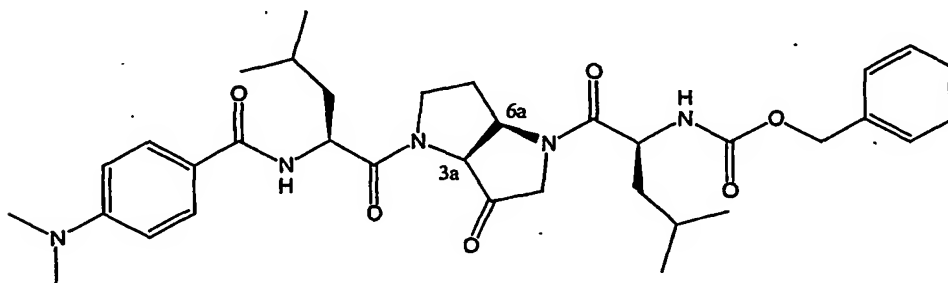
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HPLC Rt = 21.8-22.9 mins (> 80%), HPLC-MS 594.1 [M + H]⁺.

10

EXAMPLE 37. (3a*S*, 6a*R*)-((1*S*)-1-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-carbamic acid benzyl ester



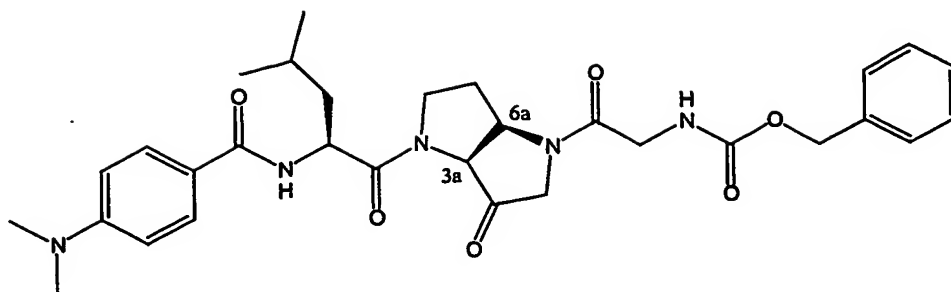
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HPLC Rt = 17.15 mins (> 85%), HPLC-MS 634.3 [M + H]⁺.

EXAMPLE 38. (3a*S*, 6a*R*)-(2-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl}-2-oxo-ethyl)-carbamic acid benzyl ester

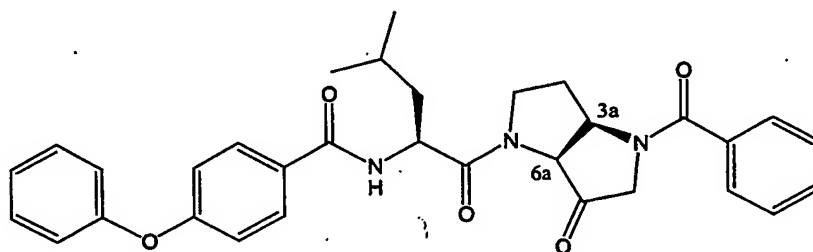
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-327-



HPLC Rt = 13.79 mins (> 85%), HPLC-MS 578.3 [M + H]⁺.

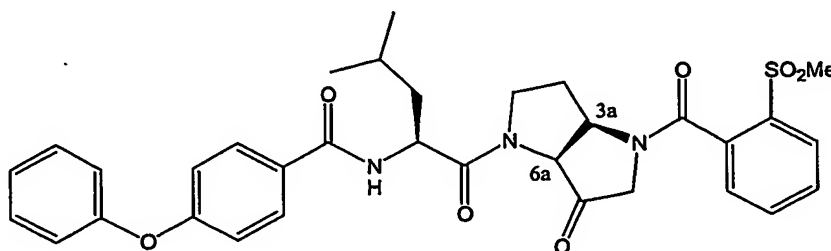
- 5 EXAMPLE 39. (3aR, 6aS)-N-[(1S)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-phenoxy-benzamide



- 10 HPLC Rt = 17.5-18.2 mins (> 75%), HPLC-MS 540.2 [M + H]⁺.

EXAMPLE 40. (3aR, 6aS)-N-[(1S)-1-[4-(2-Methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl]-4-phenoxy-benzamide

15

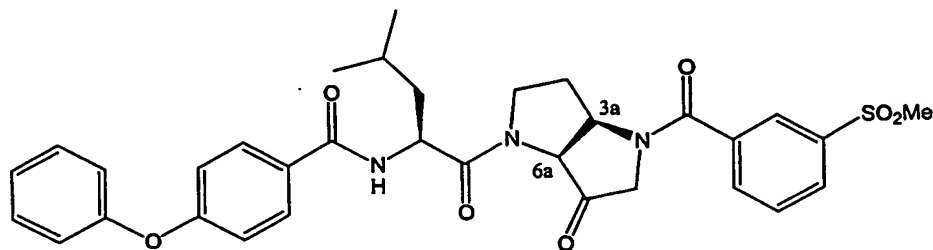


HPLC Rt = 16.9-17.9 mins (> 75%), HPLC-MS 618.2 [M + H]⁺, 636.2 [M + H + H₂O]⁺.

-328-

EXAMPLE 41. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(3-Methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-phenoxy-benzamide

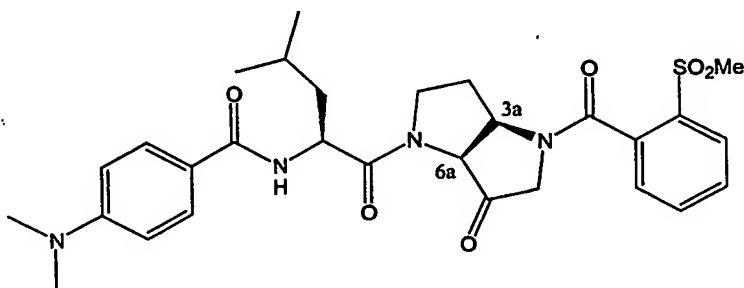
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HPLC R_t = 16.6-17.7 mins (> 70%), HPLC-MS 618.2 $[M + H]^+$.

10

EXAMPLE 42. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(2-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide



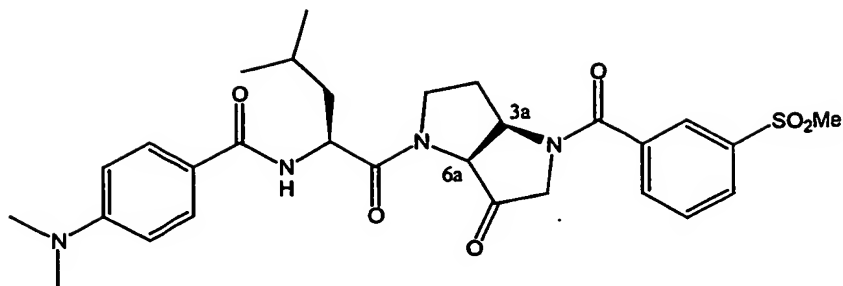
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HPLC R_t = 13.10 mins (> 90%), HPLC-MS 569.3 $[M + H]^+$, 1159.4 $[2M + Na]^+$.

20

EXAMPLE 43. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(3-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

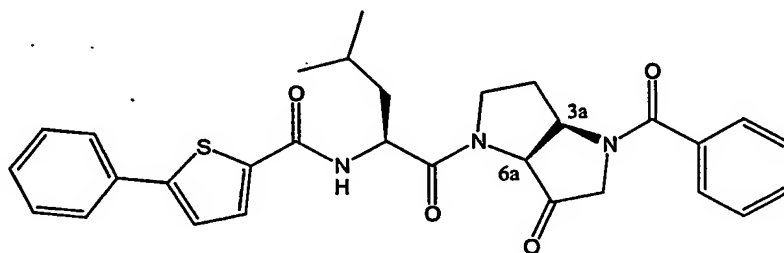
-329-



HPLC Rt = 11.59 mins (> 95%), HPLC-MS 569.2 [M + H]⁺, 587.2 [M + H + H₂O]⁺.

5

EXAMPLE 44. (3a*R*, 6a*S*)-5-Phenyl-thiophene-2-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide

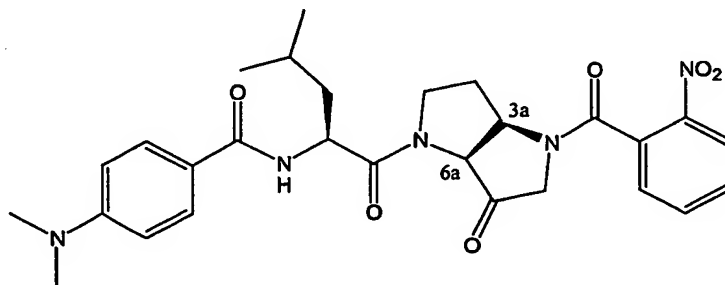


10

HPLC Rt = 17.2-18.1 mins (> 75%), HPLC-MS 530.2 [M + H]⁺.

EXAMPLE 45. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(2-nitro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

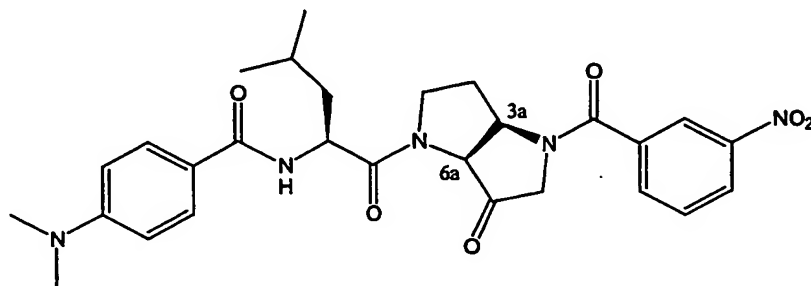
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-330-

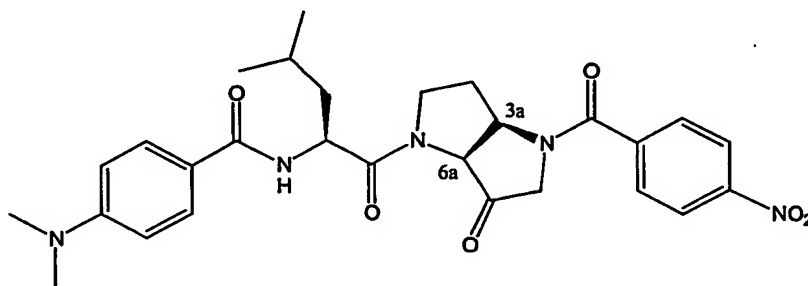
HPLC Rt = 12.47 mins (> 95%), HPLC-MS 536.2 [M + H]⁺, 554.2 [M + H + H₂O]⁺.

EXAMPLE 46. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(3-nitro-
5 benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



HPLC Rt = 13.17 mins (> 90%), HPLC-MS 536.2 [M + H]⁺, 554.2 [M + H + H₂O]⁺.

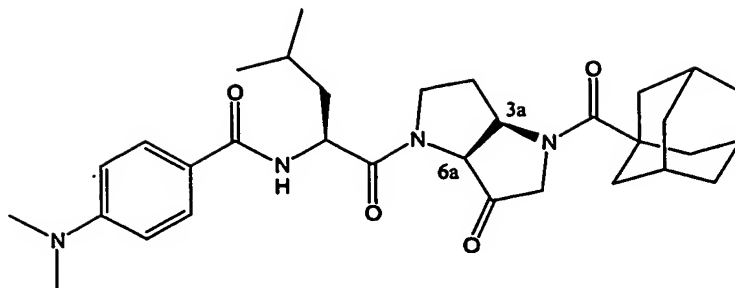
EXAMPLE 47. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(4-nitro-
15 benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



HPLC Rt = 13.19 mins (> 95%), HPLC-MS 536.2 [M + H]⁺, 554.2 [M + H + H₂O]⁺.

EXAMPLE 48. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(Adamantane-1-carbonyl)-6-oxo-
20 hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-
benzamide

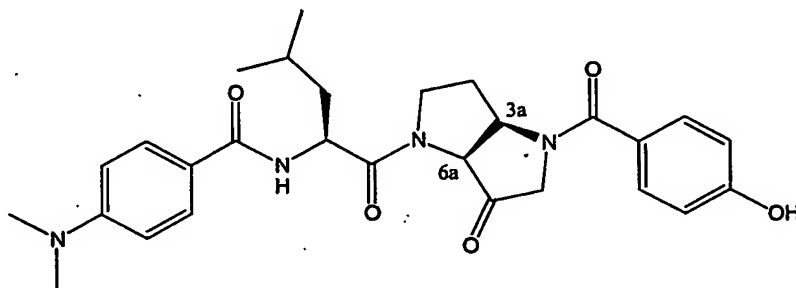
-331-



HPLC Rt = 16.4-17.1 mins (> 50%), HPLC-MS 549.3 [M + H]⁺.

5

EXAMPLE 49. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(4-hydroxy-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

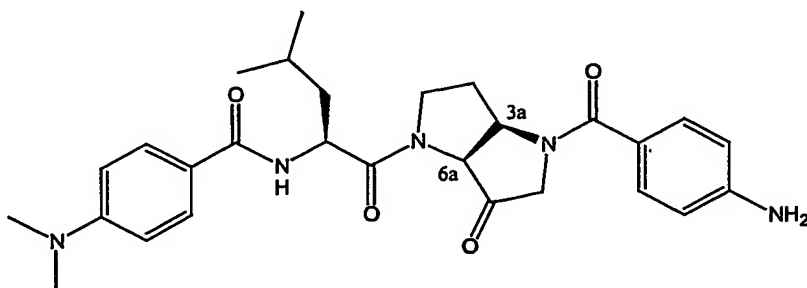


10

HPLC Rt = 11.05 mins (> 90%), HPLC-MS 507.2 [M + H]⁺, 525.2 [M + H + H₂O]⁺.

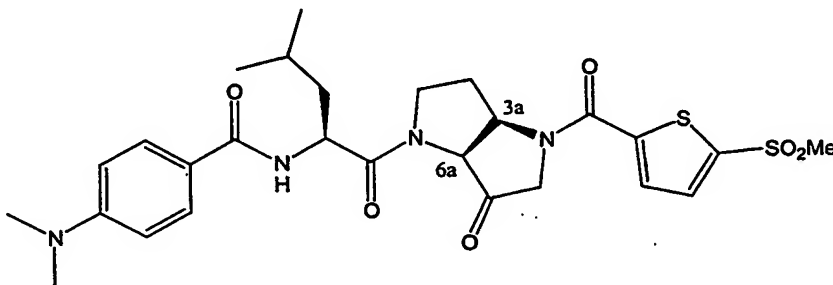
EXAMPLE 50. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(4-Amino-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

15



HPLC Rt = 9.33 mins (> 85%), HPLC-MS 506.2 [M + H]⁺, 524.2 [M + H + H₂O]⁺.

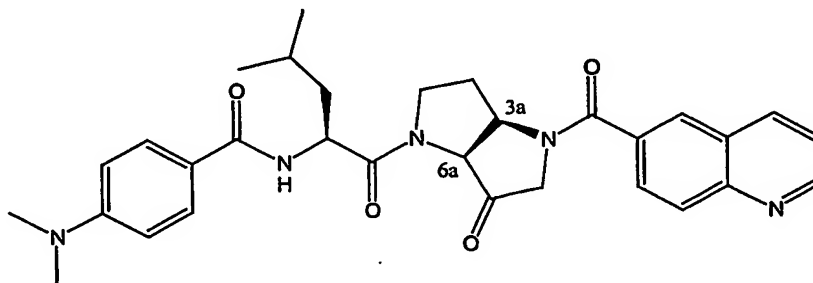
5 **EXAMPLE 51. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(5-methanesulfonylthiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide**



10

HPLC Rt = 12.10 mins (> 95%), HPLC-MS 575.1 [M + H]⁺, 593.1 [M + H + H₂O]⁺.

15. **EXAMPLE 52. (3aR, 6aS)-4-Dimethylamino-N-((1S)-3-methyl-1-[6-oxo-4-(quinoline-6-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl)-benzamide**

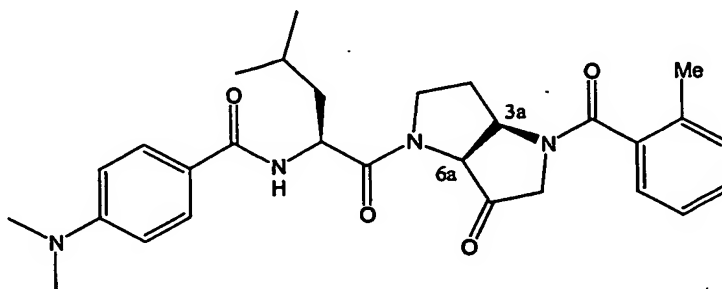


20

HPLC Rt = 9.99 mins (> 85%), HPLC-MS 542.2 [M + H]⁺, 560.2 [M + H + H₂O]⁺.

-333-

EXAMPLE 53. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(2-methylbenzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

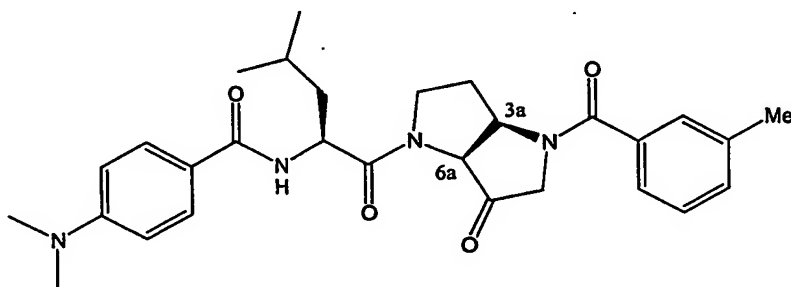


5

HPLC Rt = 13.08 mins (> 90%), HPLC-MS 505.2 [M + H]⁺, 523.2 [M + H + H₂O]⁺.

EXAMPLE 54. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(3-methylbenzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

10

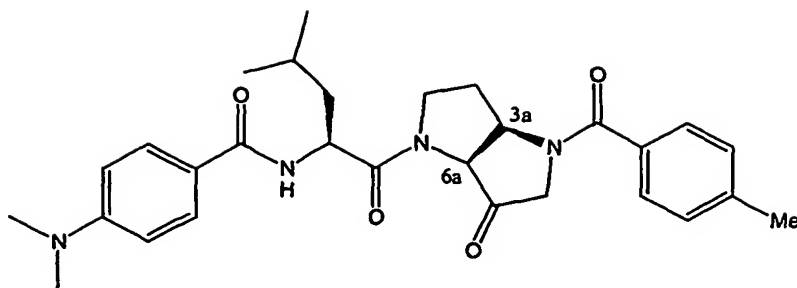


15

HPLC Rt = 13.12 mins (> 85%), HPLC-MS 505.2 [M + H]⁺, 523.2 [M + H + H₂O]⁺.

EXAMPLE 55. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(4-methylbenzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

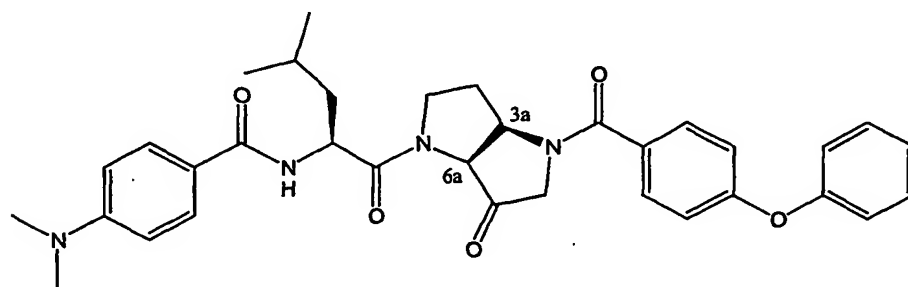
-334-



HPLC Rt = 13.65 mins (> 90%), HPLC-MS 505.2 [M + H]⁺, 523.2 [M + H + H₂O]⁺.

5

EXAMPLE 56. (3aR, 6aS)-4-Dimethylamino-N-((1S)-3-methyl-1-[6-oxo-4-(4-phenoxymethyl)-4-phenoxymethyl]-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl)-benzamide

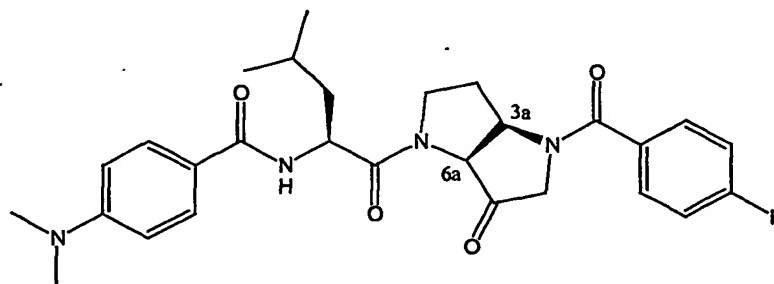


10

HPLC Rt = 16.38 mins (> 80%), HPLC-MS 583.2 [M + H]⁺.

EXAMPLE 57. (3aR, 6aS)-4-Dimethylamino-N-((1S)-1-[4-(4-fluorobenzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-benzamide

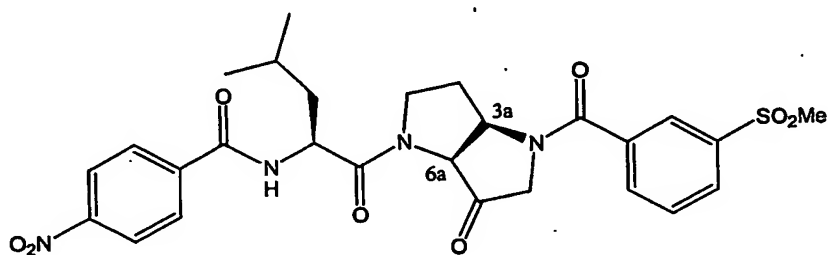
15



-335-

HPLC Rt = 12.83 mins (> 90%), HPLC-MS 509.1 [M + H]⁺, 527.1 [M + H + H₂O]⁺.

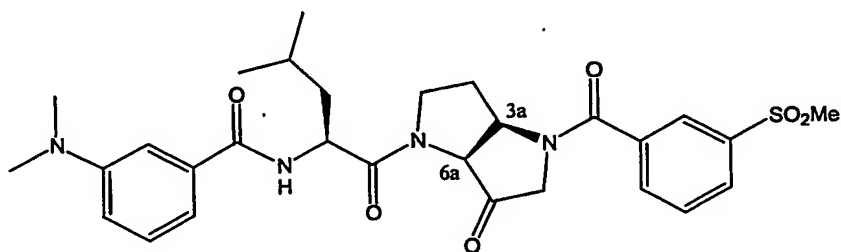
5 EXAMPLE 58. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(3-Methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-nitro-benzamide



10 HPLC Rt = 13.37 mins (> 95%), HPLC-MS 571.1 [M + H]⁺.

EXAMPLE 59. (3a*R*, 6a*S*)-3-Dimethylamino-*N*-{(1*S*)-1-[4-(3-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

15

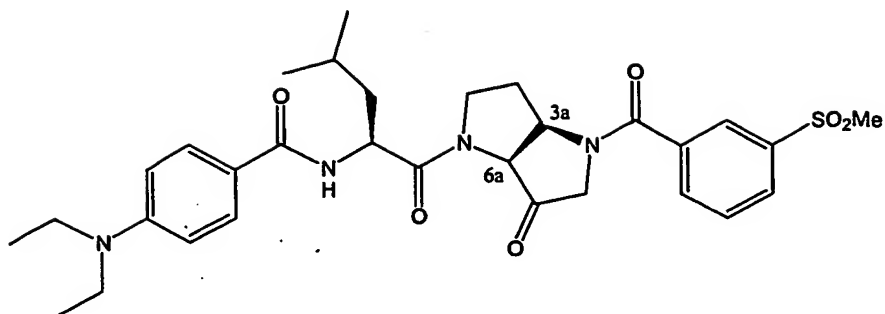


HPLC Rt = 10.29 mins (> 85%), HPLC-MS 569.1 [M + H]⁺, 587.2 [M + H + H₂O]⁺.

20

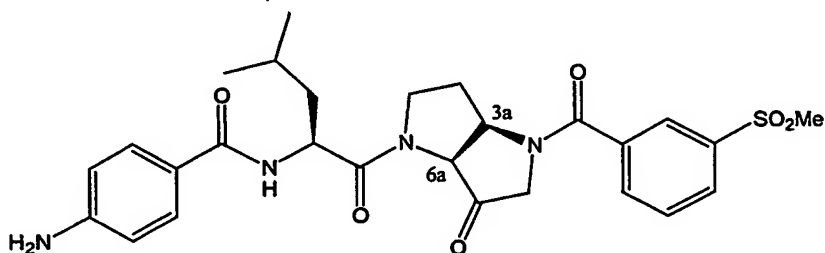
EXAMPLE 60. (3a*R*, 6a*S*)-4-Diethylamino-*N*-{(1*S*)-1-[4-(3-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

-336-



5 HPLC Rt = 11.13 mins (> 90%), HPLC-MS 597.2 [M + H]⁺, 615.2 [M + H + H₂O]⁺.

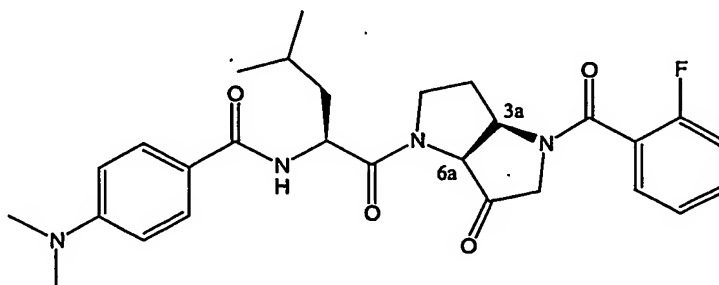
EXAMPLE 61. (3aR, 6aS)-4-Amino-N-{(1S)-1-[4-(3-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide



10

HPLC Rt = 9.69 mins (> 80%), HPLC-MS 541.1 [M + H]⁺.

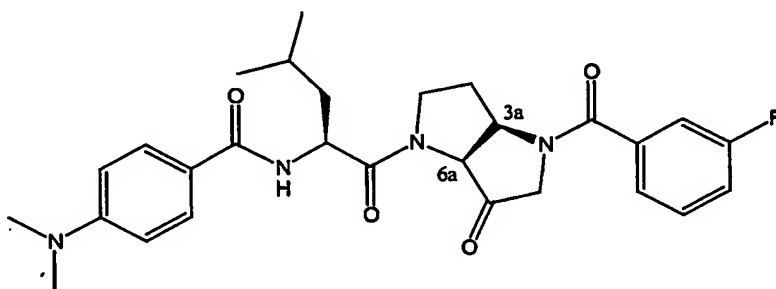
15 EXAMPLE 62. (3aR, 6aS)-4-Dimethylamino-N-{(1S)-1-[4-(2-fluoro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide



-337-

HPLC Rt = 9.18 mins (> 95%), HPLC-MS 509.2 [M + H]⁺, 527.2 [M + H + H₂O]⁺.

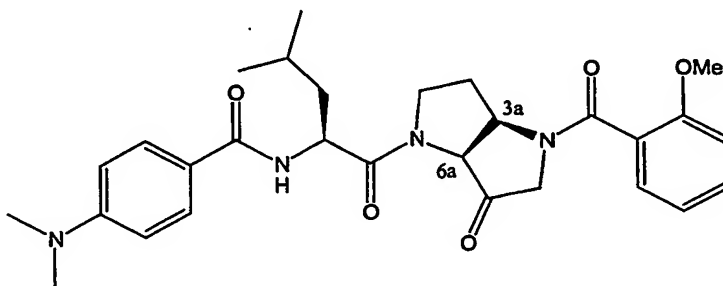
- 5 EXAMPLE 63. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(3-fluoro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide



- 10 HPLC Rt = 10.59 mins (> 90%), HPLC-MS 509.2 [M + H]⁺, 527.2 [M + H + H₂O]⁺.

EXAMPLE 64. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(2-methoxy-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

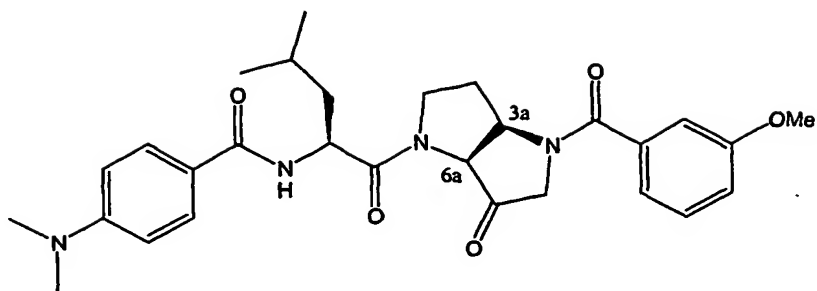
15



HPLC Rt = 11.20 mins (> 95%), HPLC-MS 521.2 [M + H]⁺.

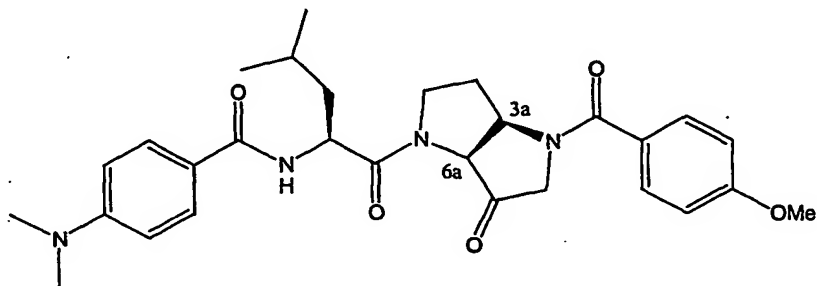
- 20 EXAMPLE 65. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(3-methoxy-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

-338-



HPLC Rt = 12.5 mins (> 90%), HPLC-MS 521.2 [M + H]⁺.

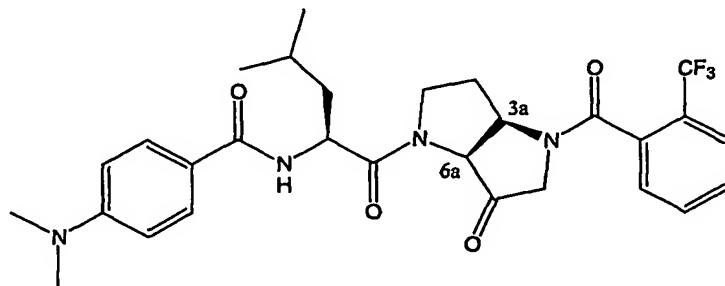
- 5 **EXAMPLE 66.** (3aR, 6aS)-4-Dimethylamino-N-((1S)-1-[4-(4-methoxy-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-benzamide



- 10 HPLC Rt = 13.33 mins (> 95%), HPLC-MS 521.1 [M + H]⁺.

EXAMPLE 67. (3aR, 6aS)-4-Dimethylamino-N-((1S)-3-methyl-1-[6-oxo-4-(2-trifluoromethyl-benzoyl)-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl)-benzamide

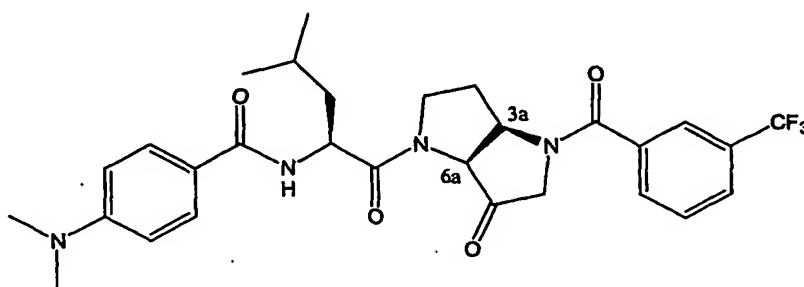
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-339-

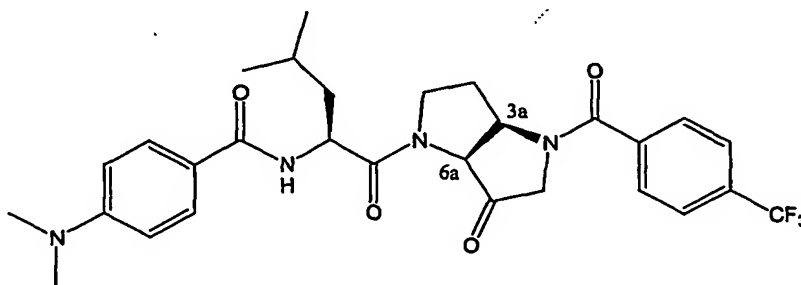
HPLC Rt = 10.98 mins (> 95%), HPLC-MS 559.2 [M + H]⁺, 577.2 [M + H + H₂O]⁺.

5 EXAMPLE 68. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(3-trifluoromethyl-benzoyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



10 HPLC Rt = 12.11 mins (> 95%), HPLC-MS 559.2 [M + H]⁺, 577.2 [M + H + H₂O]⁺.

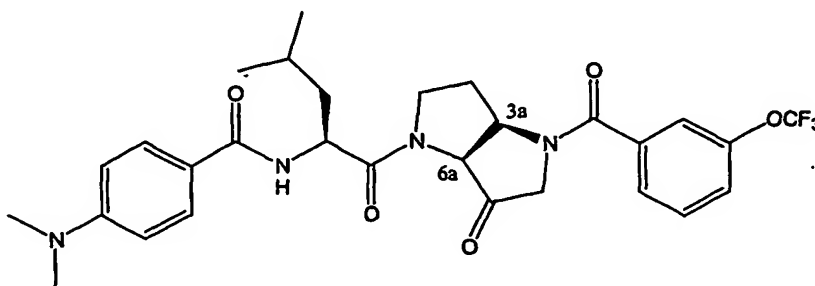
15 EXAMPLE 69. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(4-trifluoromethyl-benzoyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



20 HPLC Rt = 9.76 mins (> 95%), HPLC-MS 559.2 [M + H]⁺, 577.2 [M + H + H₂O]⁺.

-340-

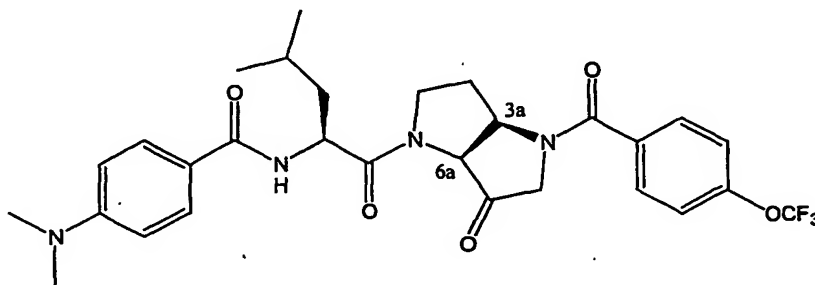
EXAMPLE 70. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(3-trifluoromethoxy-benzoyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



5

HPLC Rt = 10.42 mins (> 95%), HPLC-MS 575.2 [M + H]⁺, 593.2 [M + H + H₂O]⁺.

10 EXAMPLE 71. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(4-trifluoromethoxy-benzoyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

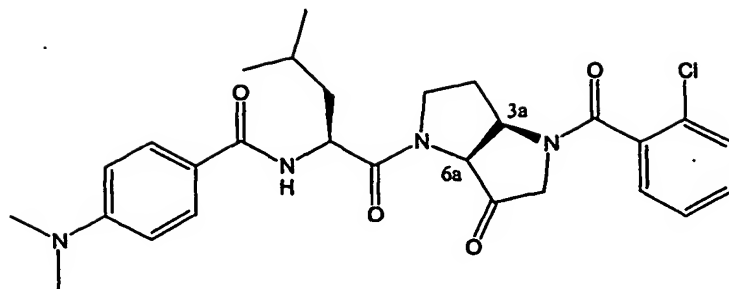


15

HPLC Rt = 10.48 mins (> 95%), HPLC-MS 575.2 [M + H]⁺, 593.2 [M + H + H₂O]⁺.

20 EXAMPLE 72. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(2-Chloro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

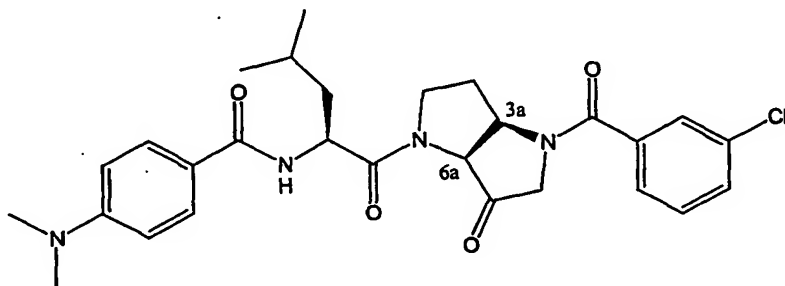
-341-



HPLC R_t = 9.99 mins (> 95%), HPLC-MS 525.2 / 527.2 $[M + H]^+$, 543.2 / 545.2 $[M + H + H_2O]^+$.

5

EXAMPLE 73. (3aR, 6aS)-N-((1S)-1-[4-(3-Chloro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-4-dimethylamino-benzamide

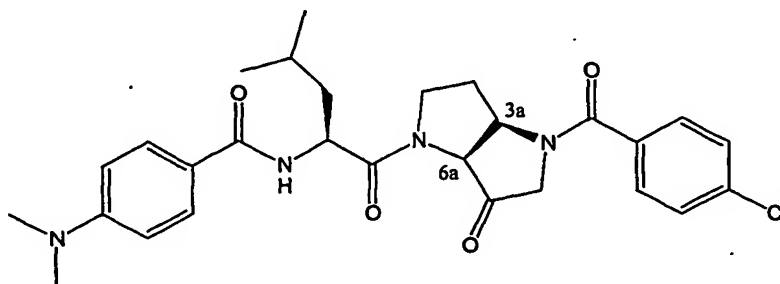


10

HPLC R_t = 11.08 mins (> 95%), HPLC-MS 525.2 / 527.2 $[M + H]^+$, 543.2 / 545.2 $[M + H + H_2O]^+$.

EXAMPLE 74. (3aR, 6aS)-N-((1S)-1-[4-(4-Chloro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-4-dimethylamino-benzamide

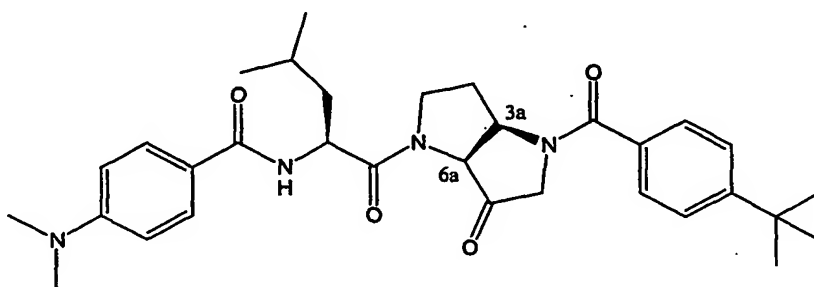
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-342-

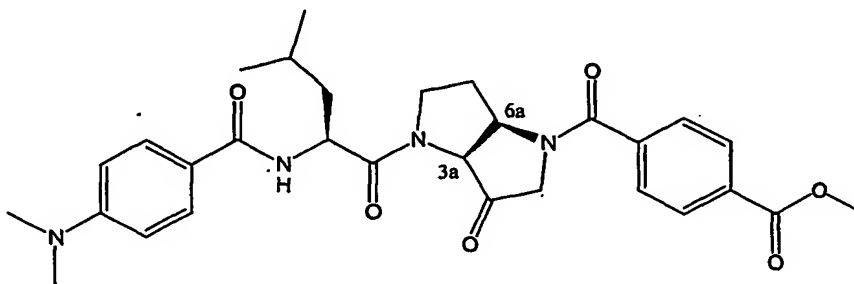
HPLC Rt = 11.03 mins (> 95%), HPLC-MS 525.2 / 527.2 $[M + H]^+$, 543.2 / 545.2 $[M + H + H_2O]^+$.

5 EXAMPLE 75. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(4-*tert*-Butyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



10 HPLC Rt = 11.51 mins (> 95%), HPLC-MS 547.3 $[M + H]^+$.

EXAMPLE 76. (3a*S*, 6a*R*)-4-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-benzoic acid methyl ester

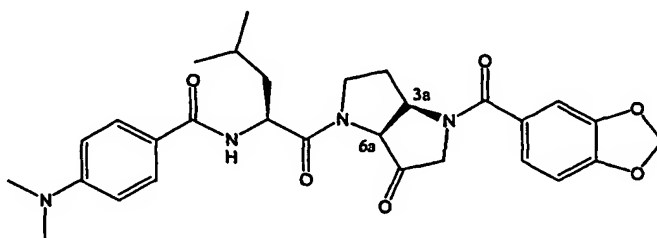


HPLC Rt = 9.76 mins (> 95%), HPLC-MS 549.2 $[M + H]^+$, 567.2 $[M + H + H_2O]^+$.

20

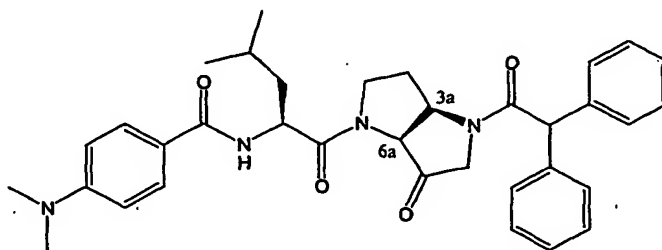
-343-

EXAMPLE 77. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(Benzo[1,3]dioxole-5-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



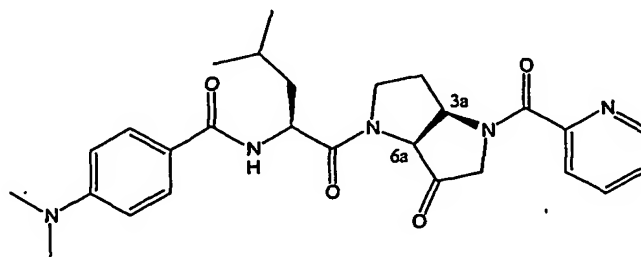
HPLC Rt = 12.3 mins (> 90%), HPLC-MS 535.2 [M + H]⁺.

EXAMPLE 78. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-[(1*S*)-1-(4-diphenylacetyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide



HPLC Rt = 14.0-15.1 mins (> 85%), HPLC-MS 581.2 [M + H]⁺.

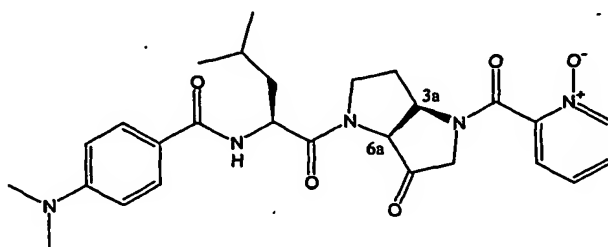
EXAMPLE 79. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



-344-

HPLC Rt = 6.17 mins (> 95%), HPLC-MS 492.2 [M + H]⁺.

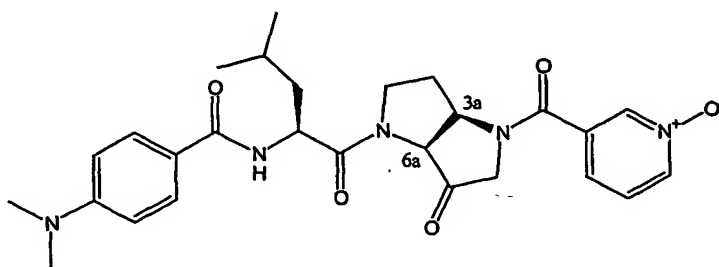
5 EXAMPLE 80. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(1-oxy-pyridine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



10 HPLC Rt = 5.82 mins (> 75%), HPLC-MS 508.2 [M + H]⁺.

Oxidation of the intermediate was performed as detailed in the general solid phase methods prior to compound release from the solid phase.

15 EXAMPLE 81. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(1-oxy-pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



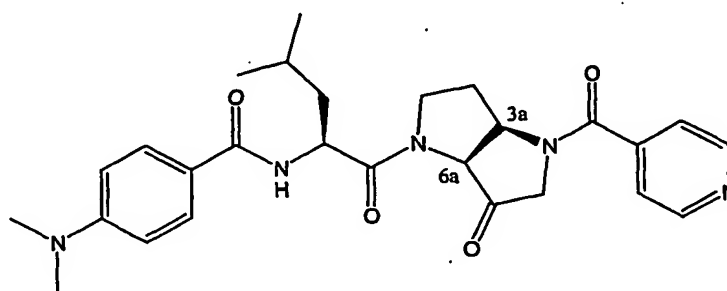
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HPLC Rt = 4.7 mins (> 95%), HPLC-MS 508.2 [M + H]⁺, 526.2 [M + H + H₂O]⁺.

-345-

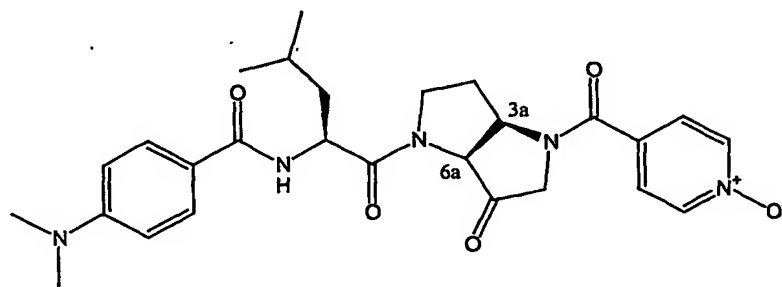
Oxidation of the intermediate was performed as detailed in the general solid phase methods prior to compound release from the solid phase.

5 EXAMPLE 82. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



10 HPLC *R*_t = 4.5 mins (> 95%), HPLC-MS 492.2 [M + H]⁺, 510.2 [M + H + H₂O]⁺.

EXAMPLE 83. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(1-oxy-pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

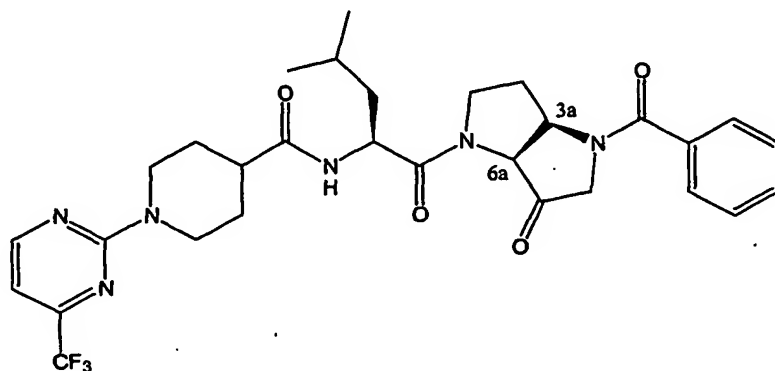


HPLC *R*_t = 4.9 mins (> 95%), HPLC-MS 508.2 [M + H]⁺, 526.2 [M + H + H₂O]⁺.

20 Oxidation of the intermediate was performed as detailed in the general solid phase methods prior to compound release from the solid phase.

-346-

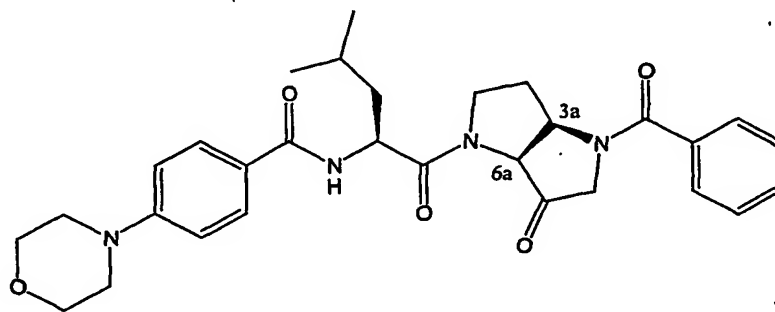
EXAMPLE 84. (3a*R*, 6a*S*)-1-(4-Trifluoromethyl-pyrimidin-2-yl)-piperidine-4-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide



HPLC Rt = 16.49 mins (> 95%), HPLC-MS 601.2 [M + H]⁺.

EXAMPLE 85. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-morpholin-4-yl-benzamide

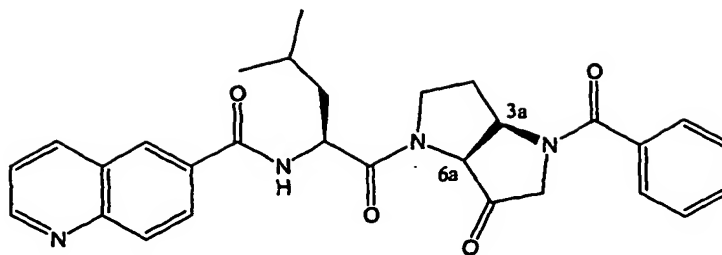
10



HPLC Rt = 9.37 mins (> 95%), HPLC-MS 533.2 [M + H]⁺.

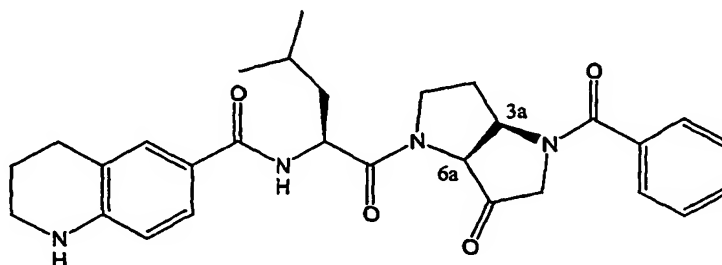
EXAMPLE 86. (3a*R*, 6a*S*)-Quinoline-6-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide

-347-



HPLC Rt = 11.73 mins (> 95%), HPLC-MS 499.2 [M + H]⁺.

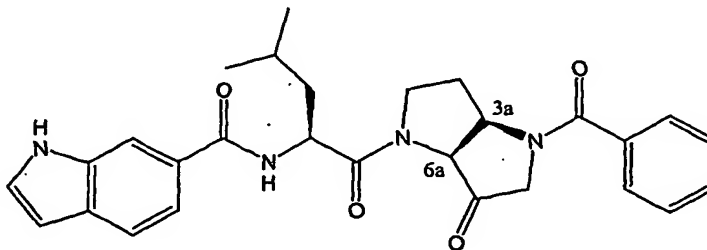
- 5 EXAMPLE 87. (3a*R*, 6a*S*)-1,2,3,4-Tetrahydro-quinoline-6-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide



10

HPLC Rt = 9.06 mins (> 95%), HPLC-MS 503.2 [M + H]⁺, 521.2 [M + H + H₂O]⁺.

- 15 EXAMPLE 88. (3a*R*, 6a*S*)-1*H*-Indole-6-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide

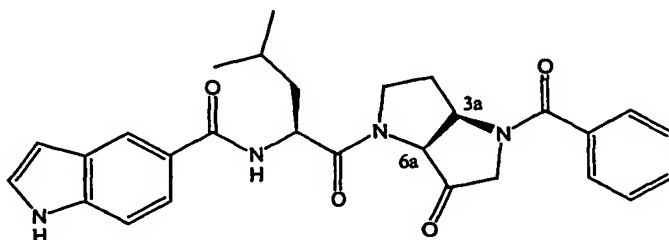


HPLC Rt = 10.13 mins (> 85%), HPLC-MS 487.1 [M + H]⁺.

-348-

EXAMPLE 89. (3a*R*, 6a*S*)-1*H*-Indole-5-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide

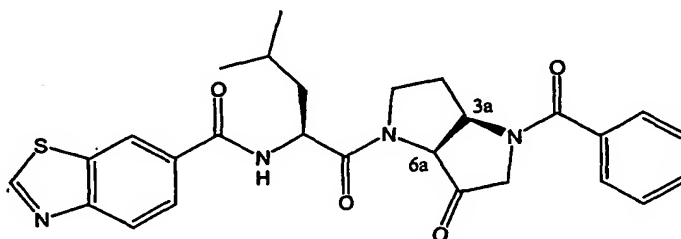
5



HPLC R_t = 9.58 mins (> 85%), HPLC-MS 487.2 $[M + H]^+$.

EXAMPLE 90. (3a*R*, 6a*S*)-Benzothiazole-6-carboxylic acid [(1*S*)-1-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide

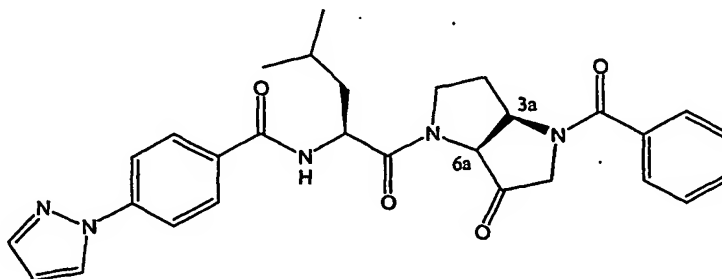
10



HPLC R_t = 14.15 mins (> 95%), HPLC-MS 505.1 $[M + H]^+$.

15

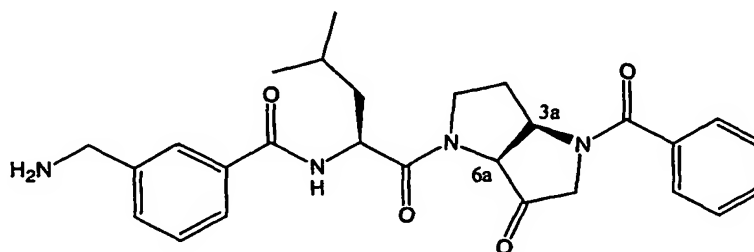
EXAMPLE 91. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-pyrazol-1-yl-benzamide



-349-

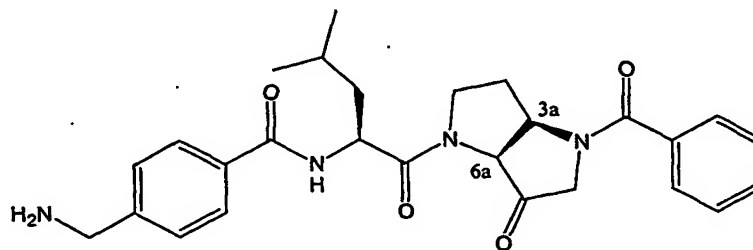
HPLC Rt = 10.25 mins (> 95%), HPLC-MS 514.2 [M + H]⁺.

EXAMPLE 92. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-[(1*S*)-1-(4-benzoyl-6-oxo-
5 hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide



HPLC Rt = 7.42 mins (> 95%), HPLC-MS 477.2 [M + H]⁺, 495.2 [M + H +
10 H₂O]⁺, 975.3 [2M + Na]⁺.

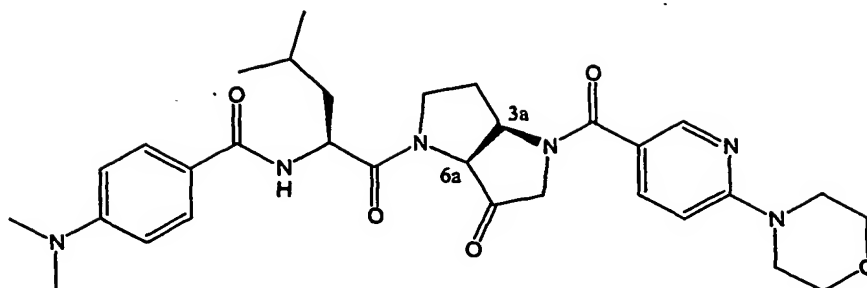
EXAMPLE 93. (3a*R*, 6a*S*)-4-Aminomethyl-*N*-[(1*S*)-1-(4-benzoyl-6-oxo-
hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide



HPLC Rt = 6.86 mins (> 95%), HPLC-MS 477.2 [M + H]⁺, 495.2 [M + H +
15 H₂O]⁺, 975.3 [2M + Na]⁺.

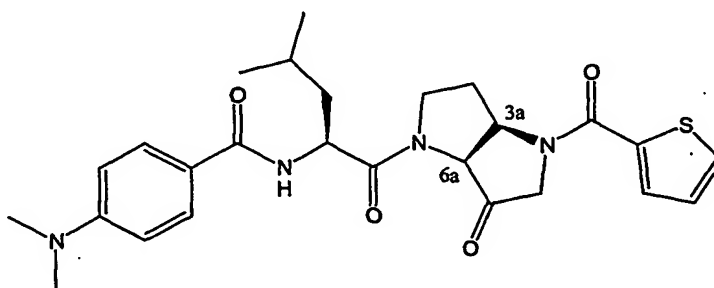
EXAMPLE 94. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(6-
20 morpholin-4-yl-pyridine-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-
carbonyl]-butyl}-benzamide

-350-



HPLC Rt = 4.4 mins (> 90%), HPLC-MS 577.2 [M + H]⁺.

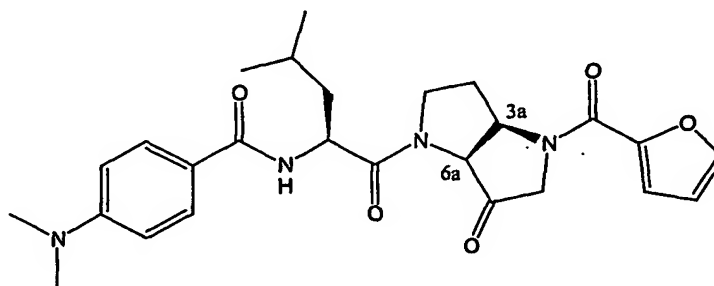
- 5 **EXAMPLE 95.** (3aR, 6aS)-4-Dimethylamino-N-((1S)-3-methyl-1-[6-oxo-4-(thiophene-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl)-benzamide



10

HPLC Rt = 7.7 mins (> 90%), HPLC-MS 497.1 [M + H]⁺.

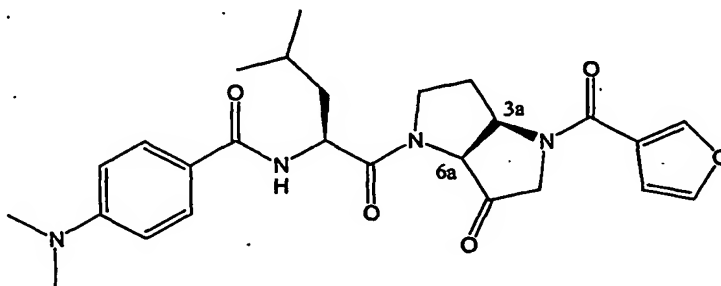
- 15 **EXAMPLE 96.** (3aR, 6aS)-4-Dimethylamino-N-((1S)-1-[4-(furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-benzamide



-351-

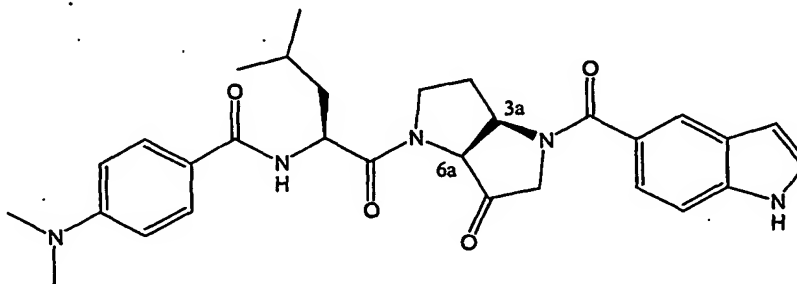
HPLC Rt = 7.3 mins (> 90%), HPLC-MS 481.2 $[M + H]^+$, 499.2 $[M + H + H_2O]^+$,
983.3 $[2M + Na]^+$.

EXAMPLE 97. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(furan-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide



HPLC Rt = 7.30 mins (> 90%), HPLC-MS 481.2 $[M + H]^+$, 499.2 $[M + H + H_2O]^+$, 983.3 $[2M + Na]^+$.

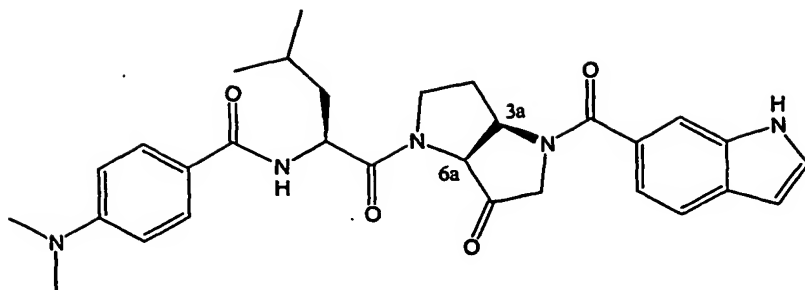
EXAMPLE 98. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(1*H*-indole-5-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide



HPLC Rt = 9.0 mins (> 80%), HPLC-MS 530.2 $[M + H]^+$.

EXAMPLE 99. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(1*H*-indole-6-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

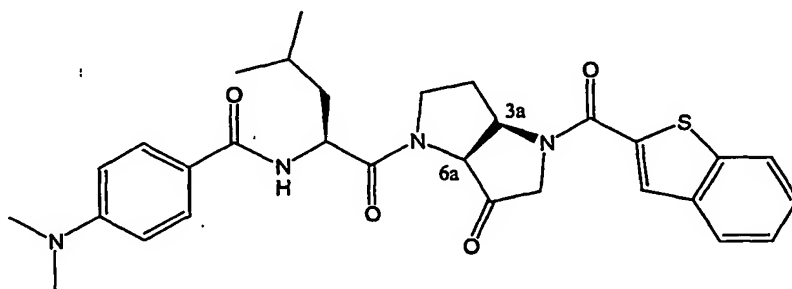
-352-



HPLC Rt = 7.8 mins (> 80%), HPLC-MS 530.2 [M + H]⁺.

5

EXAMPLE 100. (3aR, 6aS)-N-((1S)-1-[4-(Benzo[b]thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-4-dimethylamino-benzamide

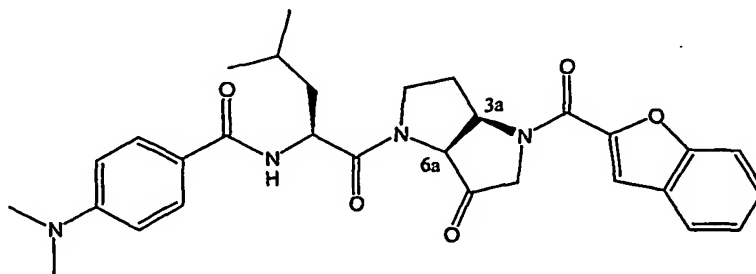


10

HPLC Rt = 12.85 mins (> 95%), HPLC-MS 547.2 [M + H]⁺.

EXAMPLE 101. (3aR, 6aS)-N-((1S)-1-[4-(Benzofuran-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-4-dimethylamino-benzamide

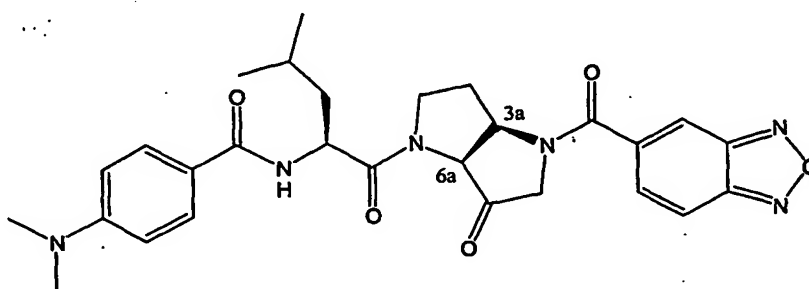
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-353-

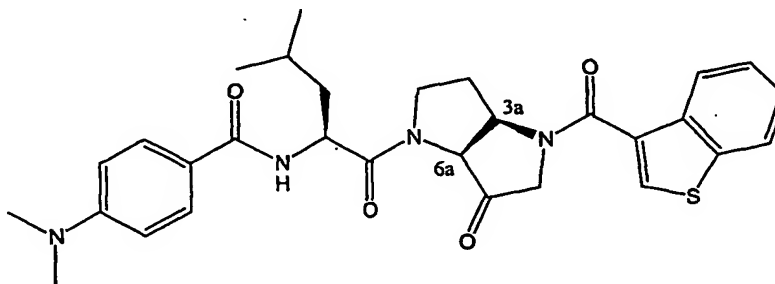
HPLC Rt = 11.9 mins (> 95%), HPLC-MS 531.2 [M + H]⁺.

5 EXAMPLE 102. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(Benzo[1,2,5]oxadiazole-5-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



10 HPLC Rt = 7.06 mins (> 90%), HPLC-MS 533.2 [M + H]⁺, 551.2 [M + H + H₂O]⁺.

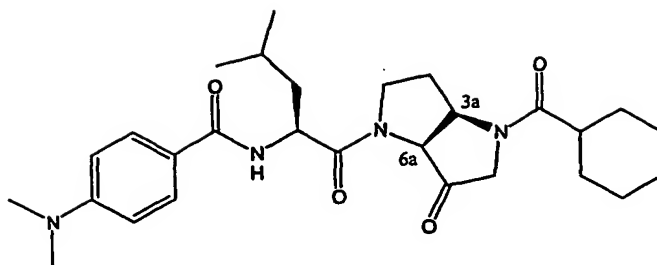
15 EXAMPLE 103. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(Benzo[*b*]thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



20 HPLC Rt = 11.8 mins (> 95%), HPLC-MS 547.2 [M + H]⁺.

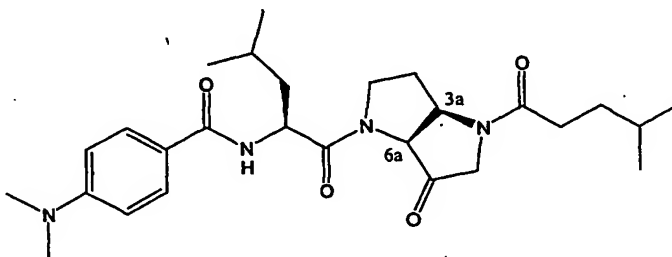
EXAMPLE 104. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl]-4-dimethylamino-benzamide

-354-



5 HPLC Rt = 12.9-13.9 mins (> 90%), HPLC-MS 497.2 [M + H]⁺, 515.2 [M + H + H₂O]⁺.

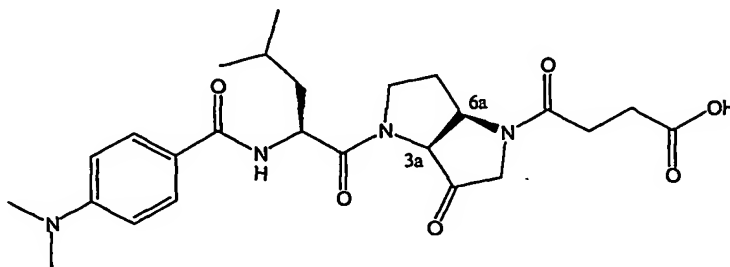
EXAMPLE 105. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



10

HPLC Rt = 13.08 mins (> 90%), HPLC-MS 485.2 [M + H]⁺, 503.2 [M + H + H₂O]⁺, 991.4 [2M + Na]⁺,

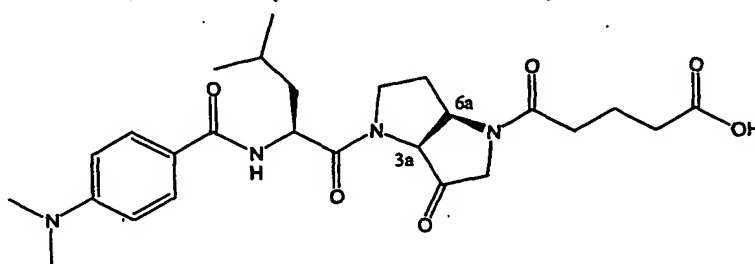
15 EXAMPLE 106. (3a*S*, 6a*R*)-4-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl}-4-oxo-butyric acid



-355-

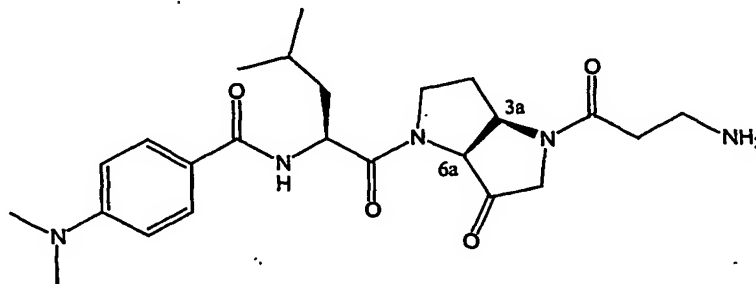
HPLC Rt = 4.35 mins (> 90%), HPLC-MS 487.2 [M + H]⁺.

EXAMPLE 107. (3a*S*, 6a*R*)-5-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl}-5-oxo-pentanoic acid



HPLC Rt = 4.99 mins (> 90%), HPLC-MS 501.2 [M + H]⁺.

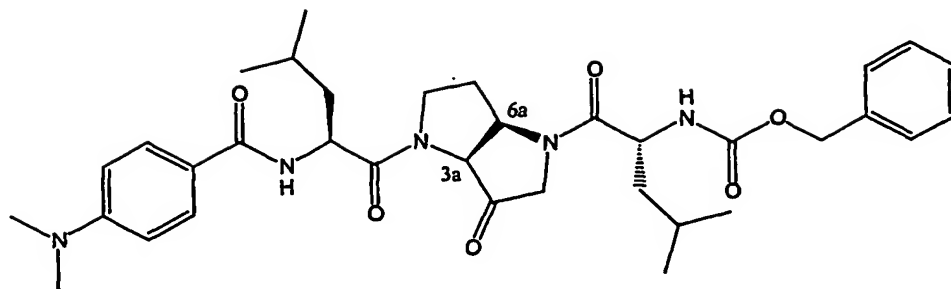
EXAMPLE 108. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(3-Amino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



HPLC Rt = 3.9 mins (> 90%), HPLC-MS 458.2 [M + H]⁺, 915.4 [2M + H]⁺.

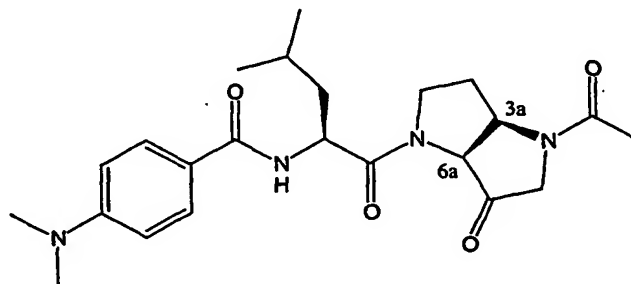
EXAMPLE 109. (3a*S*, 6a*R*)-((1*R*)-1-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-carbamic acid benzyl ester

-356-



HPLC Rt = 13.0-14.2 mins (> 90%), HPLC-MS 634.3 [M + H]⁺.

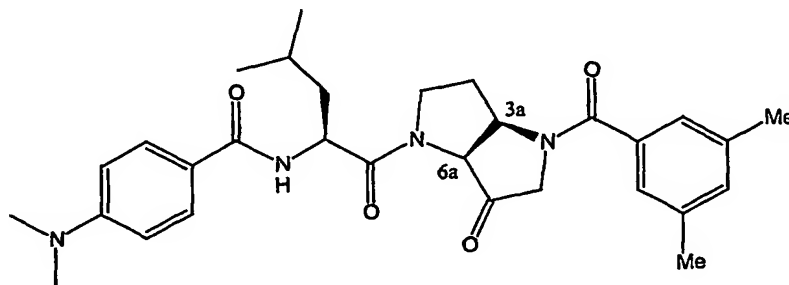
- 5 **EXAMPLE 110.** (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Acetyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-dimethylamino-benzamide



- 10 HPLC Rt = 4.58 mins (> 90%), HPLC-MS 429.2 [M + H]⁺, 451.2 [M + Na]⁺.

EXAMPLE 111. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(3,5-dimethyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

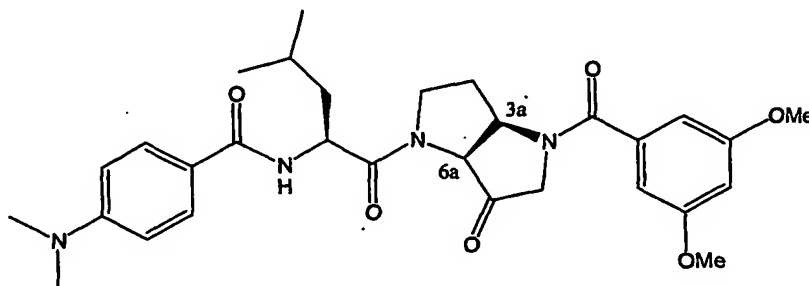
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-357-

HPLC Rt = 15.53 mins (> 90%), HPLC-MS 519.3 [M + H]⁺.

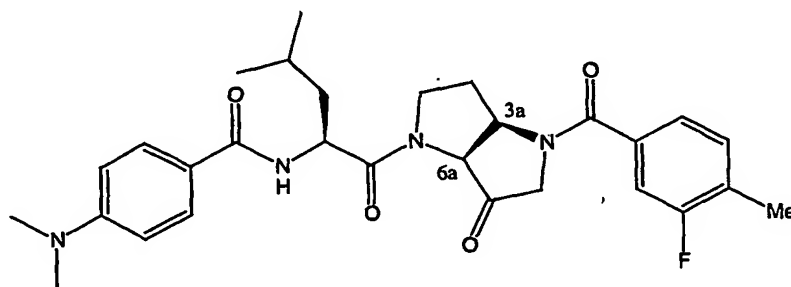
EXAMPLE 112. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(3,5-Dimethoxy-benzoyl)-6-oxo-hexahydro pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



HPLC Rt = 14.43 mins (> 90%), HPLC-MS 551.2 [M + H]⁺.

10

EXAMPLE 113. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(3-fluoro-4-methyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide



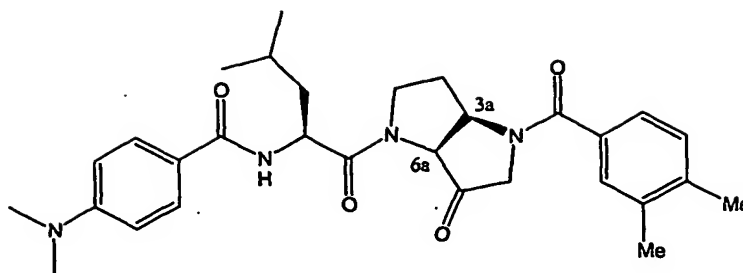
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HPLC Rt = 15.04 mins (> 95%), HPLC-MS 523.2 [M + H]⁺, 541.2 [M + H + H₂O]⁺.

20

EXAMPLE 114. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(3,4-dimethyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

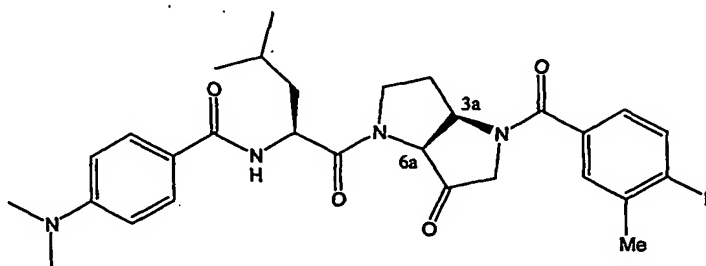
-358-



HPLC Rt = 15.70 mins (> 90%), HPLC-MS 519.3 [M + H]⁺.

5

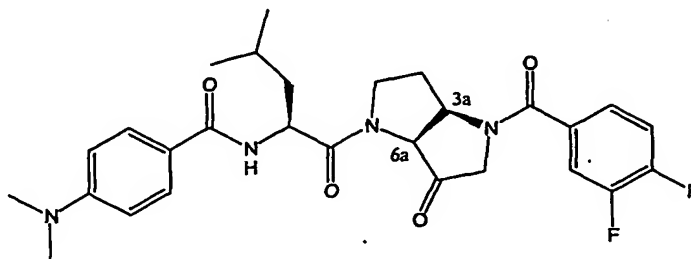
EXAMPLE 115. (3aR, 6aS)-4-Dimethylamino-N-((1S)-1-[4-(4-fluoro-3-methylbenzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-benzamide



10

HPLC Rt = 15.00 mins (> 90%), HPLC-MS 523.2 [M + H]⁺, 541.2 [M + H + H₂O]⁺.

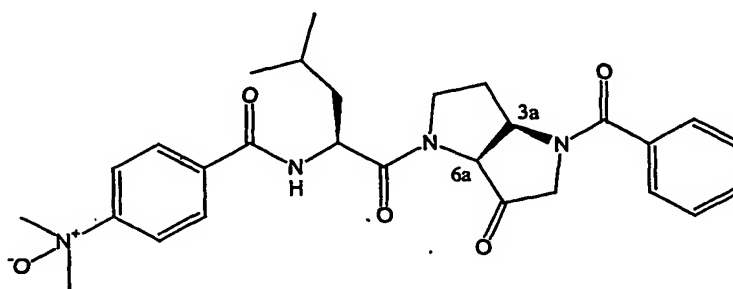
15 EXAMPLE 116. (3aR, 6aS)-N-((1S)-1-[4-(3,4-Difluoro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-4-dimethylamino-benzamide



-359-

HPLC Rt = 14.47 mins (> 90%), HPLC-MS 527.2 [M + H]⁺, 545.2 [M + H + H₂O]⁺.

5 EXAMPLE 117. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrole-1-carbonyl)-3-methyl-butyl]-4-(*N*-oxy-dimethylamino)-benzamide

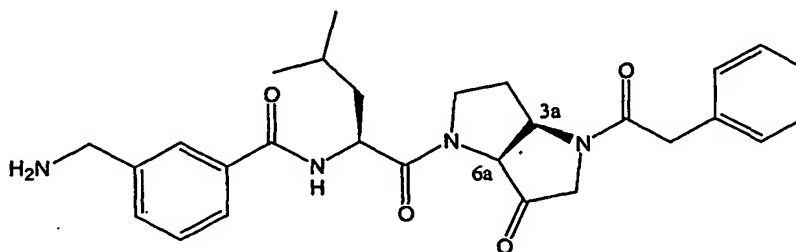


10 HPLC Rt = 11.64 mins (> 95%), HPLC-MS 507.2 [M + H]⁺, 525.2 [M + H + H₂O]⁺.

Oxidation of the intermediate was performed as detailed in the general solid phase methods prior to compound release from the solid phase.

15

EXAMPLE 118. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-[(1*S*)-3-methyl-1-(6-oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-benzamide

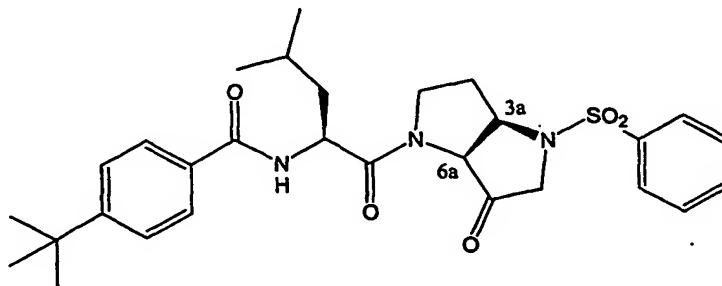


20

HPLC Rt = 12.06 mins (> 90%), HPLC-MS 491.2 [M + H]⁺, 509.2 [M + H + H₂O]⁺, 981.4 [2M + H]⁺.

-360-

EXAMPLE 119. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-*tert*-butyl-benzamide

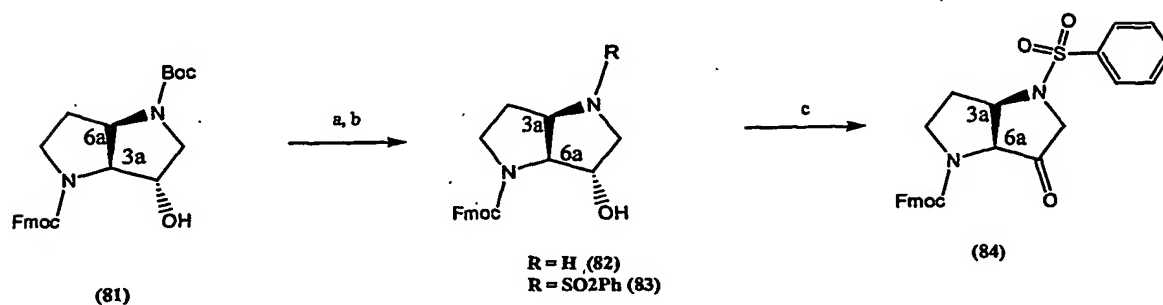


5

HPLC R_t = 21.0-22.4 mins (> 75%), HPLC-MS 540.1 $[M + H]^+$.

EXAMPLES 119-123 were prepared following the general methods detailed for EXAMPLE 1, but using an alternative building block (3a*R*, 6a*S*)-4-benzenesulfonyl-6-oxo-hexahydro-pyrrolo [3,2-*b*]pyrrole-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (84) prepared following Scheme 21.

10



15

Scheme 21. (a) 4*N* HCl in 1,4-dioxane, RT, 30mins, RT. (b) $PhSO_2Cl$, Et_3N , DCM. (c) Dess-Martin periodinane, DCM.

Preparation of (3a*R*, 6*S*, 6a*S*)-6-hydroxyhexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid 9H-fluoren-9-ylmethyl ester hydrochloride (82)

20

A solution of HCl in 1,4-dioxane (4.0*M*, 2.0 ml, 8 mmol) was added to (3*S*, 3a*S*, 6a*R*)-3-hydroxyhexahydro-pyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-*tert*-butyl

-361-

ester 4-(9H-fluoren-9-ylmethyl) ester (81) (65 mg, 0.14 mmol). The mixture was stirred in a sealed system for 50 minutes then the solvents were removed *in vacuo* to leave a residue which was azeotroped with diethyl ether (3x 10 ml) to obtain (3a*R*, 6*S*, 6a*S*)-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid 9H-fluoren-9-ylmethyl ester hydrochloride (82) as a white solid which was used without further purification (see below). HPLC-MS 351.1 [M + H]⁺, 373.1 [M + Na]⁺, 723.2 [2M + Na]⁺; HRMS C₂₁H₂₃N₂O₃Na req. 351.1708, *find.* 351.1712 (0.95ppm).

10 **Preparation of (3a*R*, 6*S*, 6a*S*)-4-benzenesulfonyl-6-hydroxyhexahydropyrrolo [3,2-*b*]pyrrole-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (83)**

Dichloromethane (1.5 ml), benzenesulfonyl chloride (20 µl, 0.16 mmol) then triethylamine (44 µl, 0.32 mmol) were added consecutively whilst stirring to (3a*R*, 6*S*, 6a*S*)-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid 9H-fluoren-9-ylmethyl ester hydrochloride (82) (prepared as above, 0.14 mmol) under an atmosphere of argon. The mixture was stirred for 1 hour then the product extracted into ethyl acetate (40 ml), washed with aqueous saturated sodium hydrogen carbonate (40 ml), pH 3 hydrochloric acid (40 ml) and brine (40 ml) then dried (Na₂SO₄), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 30 : 70 to give (3a*R*, 6*S*, 6a*S*)-4-benzenesulfonyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (83) as a white solid (60 mg, 86%). TLC (Single spot, *R_f* = 0.40, EtOAc : heptane 1 : 1), analytical HPLC single main peak *R_t* = 20.112 min; HPLC-MS 491.0 [M + H]⁺, 513.0 [M + Na]⁺; Elemental analysis C₂₇H₂₆N₂O₅S req. (*find.*) % C 66.10 (66.02), % H 5.34 (5.36), % N 5.71 (5.61); HRMS C₂₇H₂₆N₂O₅SNa req. 513.1460, *find.* 513.1489 (5.56ppm).

30 **Preparation of (3a*R*, 6a*S*)-4-benzenesulfonyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (84)**

-362-

Dess-Martin periodinane (95 mg, 0.22 mmol) was added in portions to a stirred solution of (3aR, 6S, 6aS)-4-benzenesulfonyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid 9H-fluoren-9-yl methyl ester (83) (55 mg, 0.11 mmol) in dichloromethane (1.5 ml) under an atmosphere of argon over 2 minutes. The mixture was stirred for 3.25 hours then the solvents removed *in vacuo* to obtain a residue which was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 25 : 75 to give (3aR, 6aS)-4-benzenesulfonyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (84) as a white solid (44 mg, 82%). TLC (Single spot, R_f = 0.55, EtOAc : heptane 65 : 35), analytical HPLC broad peak R_t = 20.0-21.5 min; HPLC-MS single broad main UV peak, 489.0 [M + H]⁺, 511.0 [M + Na]⁺, 529.0 [M + H₂O + Na]⁺, 999.0 [2M + Na]⁺; C₂₇H₂₄N₂O₅S.0.4CDCl₃ req.(*find.*) % C 61.36 (61.09), % H 4.51 (4.76), % N 5.22 (4.79); HRMS C₂₇H₂₄N₂O₅SNa req. 511.1304, *find.* 511.1615 (2.16ppm); d_H (500 MHz, CDCl₃) mixture of rotamers 2.10-2.28 (2H, m, PhSO₂NCHCH₂), 3.40-3.60 (2H, m, FmocNCH₂), 3.62-3.84 (2H, m, PhSO₂NCH₂), 4.16-4.46 (4H, m, FmocNCH, Fmoc-CH and Fmoc-CH₂), 4.48-4.61 (1H, m, PhSO₂NCH), 7.32-7.90 (13H, m, aromatic); d_C (125 MHz, CDCl₃) 31.72, 31.86 (PhSO₂NCHCH₂), 45.41 (FmocNCH₂), 47.15 (Fmoc-CH), 52.62 (PhSO₂NCH₂), 60.17 (PhSO₂NCH), 63.30, 63.52 (FmocNCH), 67.79, 68.12 (Fmoc-CH₂), 119.97, 120.09, 124.94, 127.07, 127.53, 127.74, 127.91, 129.65, 133.75 (aromatic CH), 141.29, 143.40, 143.58, 143.81, 144.12 (quaternary aromatic), 154.93 (NC=O), 203.85, 204.07 (C=O).

Following the general details from Scheme 6, the required bicycle building block (3aR, 6aS)-4-benzenesulfonyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (84) was converted to building block-linker construct (27) (where Pg₂ is phenylsulphonyl) as follows:

A solution of sodium acetate trihydrate (30 mg, 0.221 mmol) in water (0.3 ml) was added to a solution of (3aR, 6aS)-4-benzenesulfonyl-6-oxo-hexahydropyrrolo [3,2-*b*]pyrrole-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (84) (36 mg, 0.074mmol) and 4-

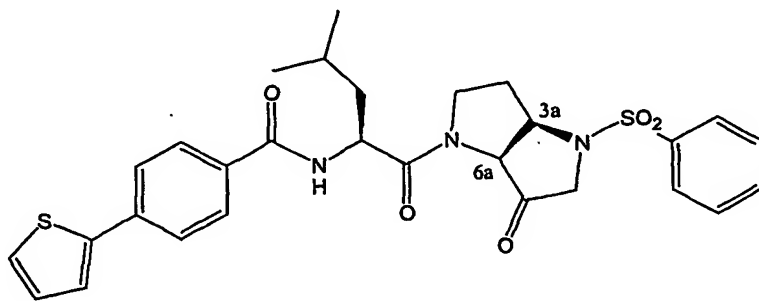
-363-

[[[(hydrazinocarbonyl)amino]methyl]cyclohexane carboxylic acid.
trifluoroacetate (Murphy, A. M., *et al*, J. Am. Chem. Soc, 114, 3156-3157,
1992) (49 mg, 0.148 mmol) in ethanol (2.1 ml). The reaction heated at 75 °C
in a sealed tube for 4.5 hour. The product was extracted into chloroform (50
ml) then washed with hydrochloric acid (0.1M, 2 x 25 ml), saturated aqueous
sodium chloride solution (30 ml) then dried (Na₂SO₄) and the solvent removed
in vacuo to leave the product as a white solid (46 mg, 91%). Analytical HPLC
has main UV peaks with Rt = 19.624 and 21.252mins and HPLC-MS (main
UV peaks each with 686.3 [M+H]⁺).

Following the general details from Scheme 6, the required building block-linker
construct (27) was attached to the solid phase providing loaded building block-
linker construct (28) following standard loading protocols and indicated
quantitative loading.

EXAMPLES 120 to 123 were prepared as detailed for EXAMPLE 119,
substituting the appropriate carboxylic acids as required;

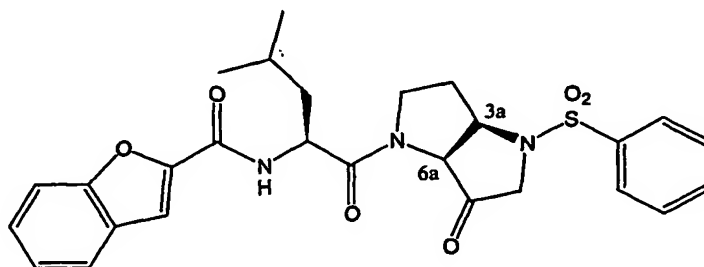
EXAMPLE 120. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzenesulfonyl-6-oxo-
hexahydropyrrolo [3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-thiophen-2-yl-
benzamide



HPLC Rt = 20.3-21.7 mins (>75 %), HPLC-MS 566.1 [M + H]⁺.

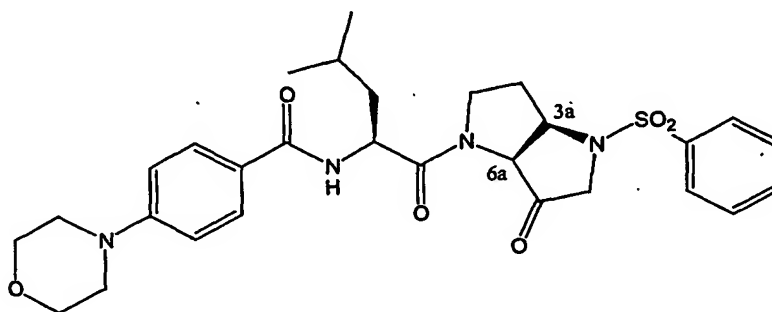
-364-

EXAMPLE 121. (3a*R*, 6a*S*)-Benzofuran-2-carboxylic acid [(1*S*)-1-(4-benzene sulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-amide



HPLC Rt = 18.3-19.9 mins (> 95%), HPLC-MS 524.1 [M + H]⁺, 546.2 [M + Na]⁺.

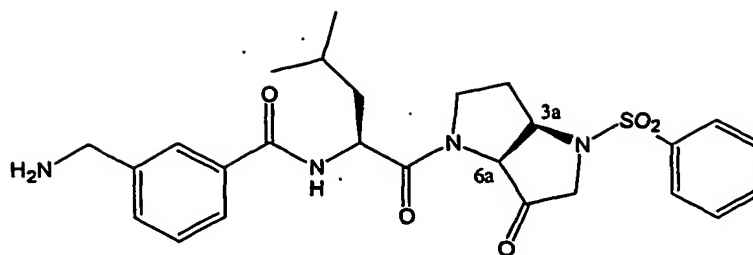
EXAMPLE 122. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzenesulfonyl-6-oxo-hexahydropyrrolo [3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-morpholin-4-yl-benzamide



HPLC Rt = 16.4-17.8 mins (> 90%), HPLC-MS 569.1 [M + H]⁺, 587.1 [M + H + H₂O]⁺.

EXAMPLE 123. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-[(1*S*)-1-(4-benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide

-365-

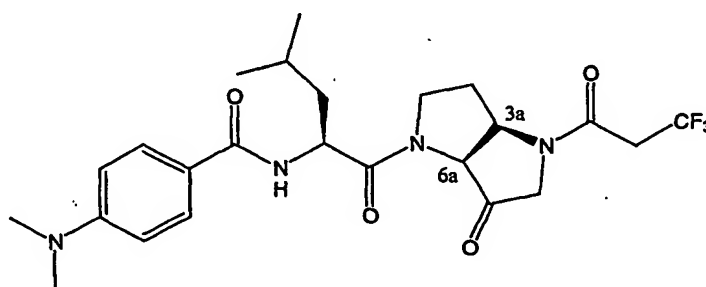


HPLC Rt = 13.0-14.1 mins (> 90%), HPLC-MS 513.1 [M + H]⁺, 531.1 [M + H + H₂O]⁺.

5

The following examples were prepared as detailed for EXAMPLE 1, substituting the appropriate carboxylic acids as required;

10 EXAMPLE 124. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(3,3,3-trifluoro-propionyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

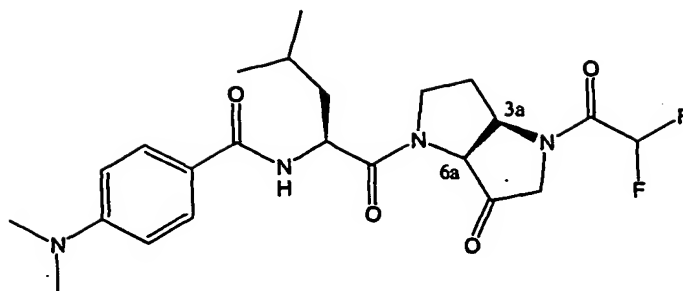


15

HPLC Rt = 10.46 mins (> 95%), HPLC-MS 497.2 [M + H]⁺, 515.2 [M + H + H₂O]⁺.

20 EXAMPLE 125. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(2,2-Difluoro-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

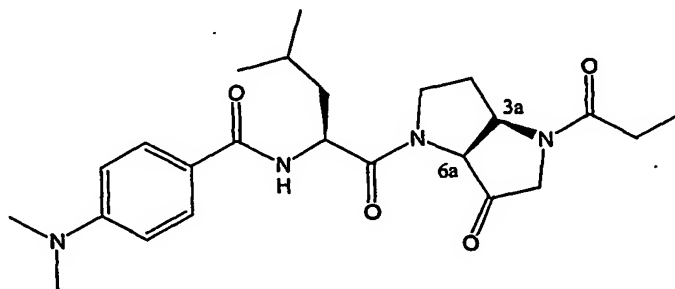
-366-



HPLC Rt = 9.31 mins (> 60%), HPLC-MS 465.1 [M + H]⁺, 483.1 [M + H + H₂O]⁺.

5

EXAMPLE 126. (3aR, 6aS)-4-Dimethylamino-N-[(1S)-3-methyl-1-(6-oxo-4-propionyl-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl)-butyl]-benzamide

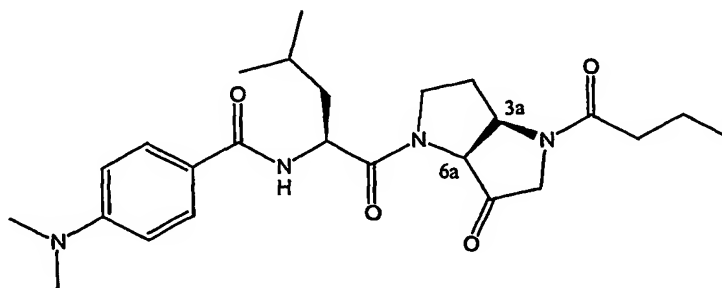


10

HPLC Rt = 9.90 mins (> 95%), HPLC-MS 443.2 [M + H]⁺, 461.2 [M + H + H₂O]⁺, 907.3 [2M + Na]⁺.

15

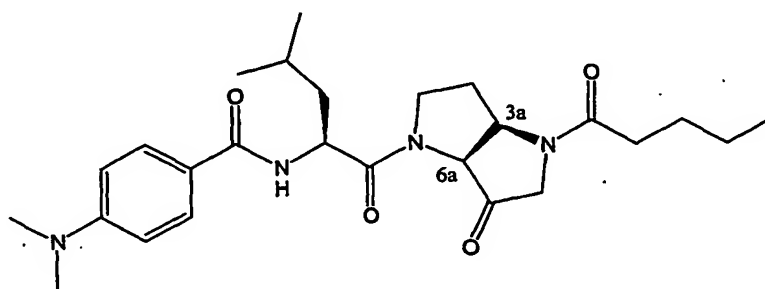
EXAMPLE 127. (3aR, 6aS)-N-[(1S)-1-(4-Butyryl-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl)-3-methyl-butyl]-4-dimethylamino-benzamide



-367-

HPLC Rt = 10.95 mins (> 90%), HPLC-MS 457.2 [M + H]⁺, 475.2 [M + H + H₂O]⁺, 935.3 [2M + Na]⁺.

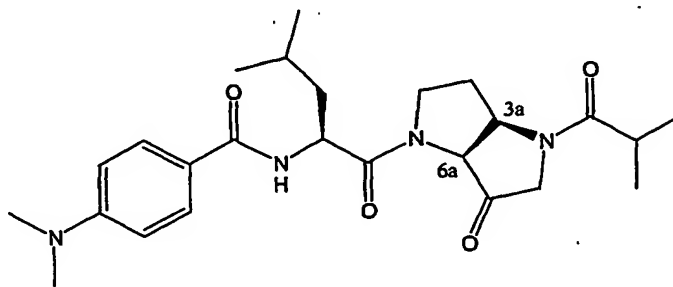
- 5 EXAMPLE 128. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-[(1*S*)-3-methyl-1-(6-oxo-4-pentanoyl-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-butyl]-benzamide



- 10 HPLC Rt = 12.0-13.1 mins (> 90%), HPLC-MS 471.2 [M + H]⁺, 489.2 [M + H + H₂O]⁺, 963.3 [2M + Na]⁺.

EXAMPLE 129. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-[(1*S*)-1-(4-isobutyryl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide

15

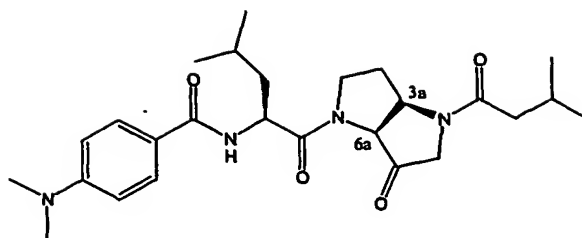


HPLC Rt = 10.55 mins (> 90%), HPLC-MS 457.2 [M + H]⁺, 475.2 [M + H + H₂O]⁺, 935.4 [2M + Na]⁺.

20

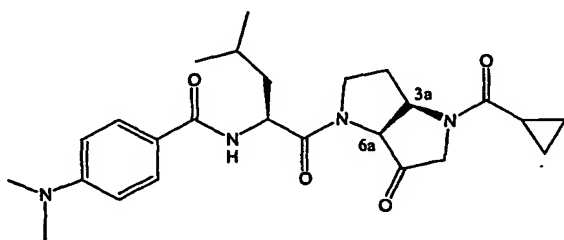
EXAMPLE 130. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(3-methyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

-368-



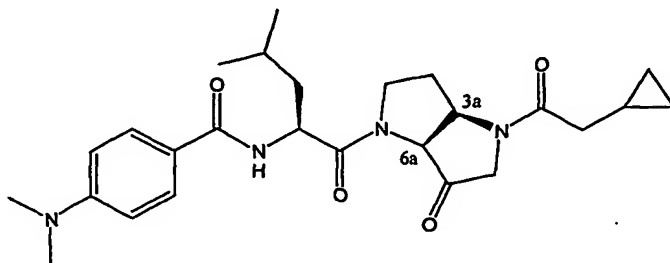
HPLC Rt = 11.81 mins (> 90%), HPLC-MS 471.2 [M + H]⁺, 489.2 [M + H + H₂O]⁺, 963.4 [2M + Na]⁺.

EXAMPLE 131. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Cyclopropanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-dimethylamino-benzamide



HPLC Rt = 10.10 mins (> 90%), HPLC-MS 455.2 [M + H]⁺, 473.2 [M + H + H₂O]⁺, 931.3 [2M + Na]⁺.

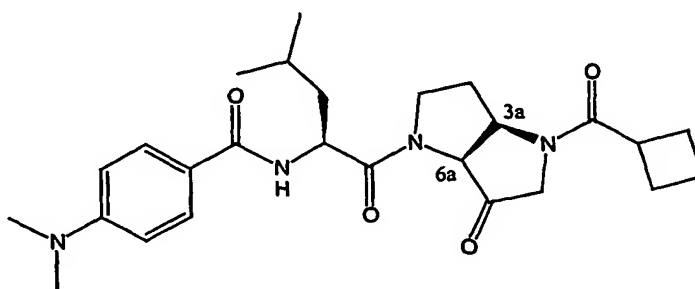
EXAMPLE 132. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(2-Cyclopropyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



-369-

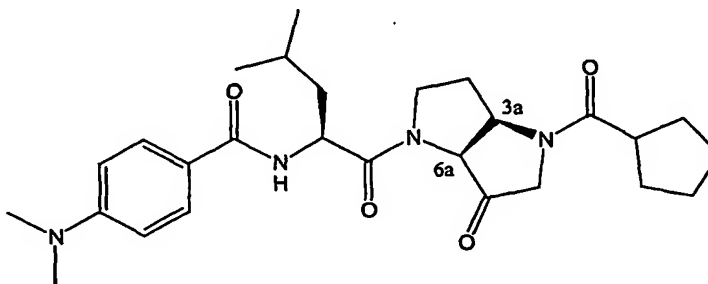
HPLC Rt = 11.13 mins (> 90%), HPLC-MS 469.2 [M + H]⁺, 487.2 [M + H + H₂O]⁺, 959.3 [2M + Na]⁺.

- 5 EXAMPLE 133. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Cyclobutanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-dimethylamino-benzamide



- 10 HPLC Rt = 11.41 mins (> 90%), HPLC-MS 469.2 [M + H]⁺, 487.2 [M + H + H₂O]⁺, 959.4 [2M + Na]⁺.

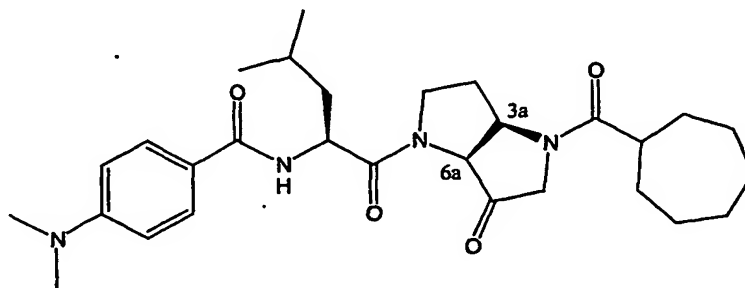
- 15 EXAMPLE 134. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Cyclopentanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-dimethylamino-benzamide



- 20 HPLC Rt = 12.2-13.1 mins (> 90%), HPLC-MS 483.2 [M + H]⁺, 501.2 [M + H + H₂O]⁺, 987.4 [2M + Na]⁺.

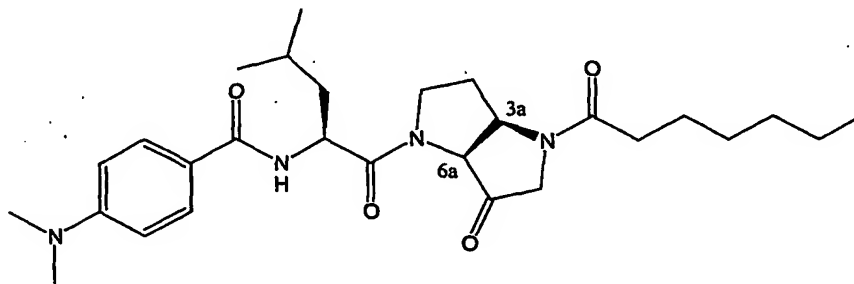
-370-

EXAMPLE 135. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Cycloheptanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-4-dimethylamino-benzamide



HPLC R_t = 14.0-14.9 mins (> 85%), HPLC-MS 511.2 $[M + H]^+$, 529.3 $[M + H + H_2O]^+$.

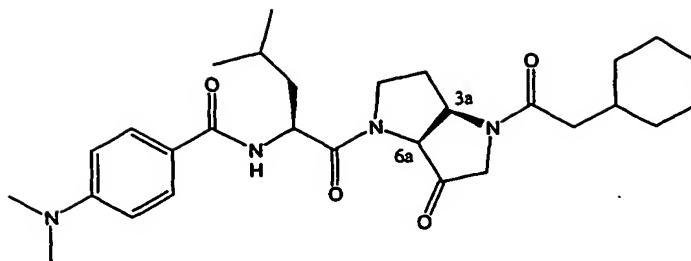
10 EXAMPLE 136. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-[(1*S*)-1-(4-heptanoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide



HPLC R_t = 14.3-15.2 mins (> 80%), HPLC-MS 499.2 $[M + H]^+$, 517.2 $[M + H + H_2O]^+$.

20 EXAMPLE 137. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(2-Cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

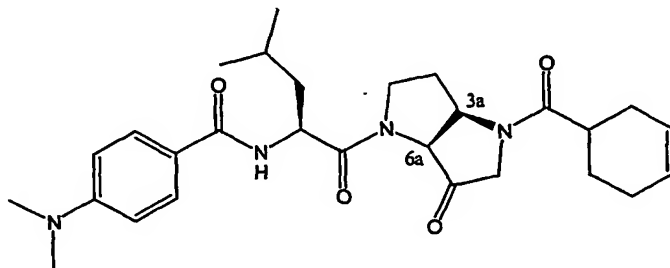
-371-



HPLC Rt = 14.27 mins (> 80%), HPLC-MS 511.2 [M + H]⁺, 529.3 [M + H + H₂O]⁺.

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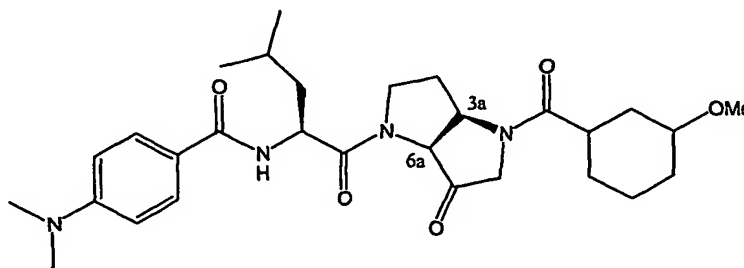
EXAMPLE 138. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(Cyclohex-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



10

HPLC Rt = 12.2-13.3 mins (> 80%), HPLC-MS 495.2 [M + H]⁺, 513.2 [M + H + H₂O]⁺.

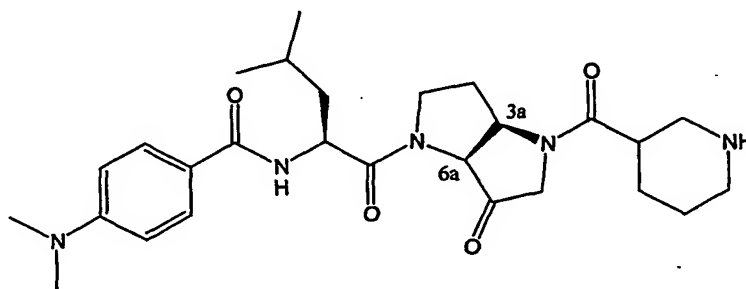
15 EXAMPLE 139. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(3-methoxycyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide



-372-

HPLC Rt = 11.1-12.8 mins (> 90%), HPLC-MS 527.2 [M + H]⁺, 545.3 [M + H + H₂O]⁺.

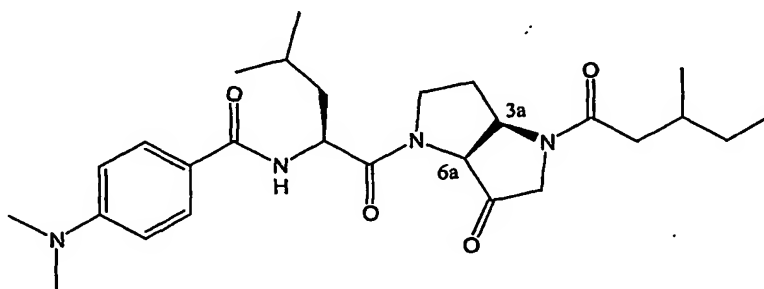
- 5 EXAMPLE 140. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(piperidine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



10

HPLC Rt = 7.8-9.3 mins (> 75%), HPLC-MS 498.2 [M + H]⁺, 516.2 [M + H + H₂O]⁺, 995.5 [2M + H]⁺.

- 15 EXAMPLE 141. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(3-methylpentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

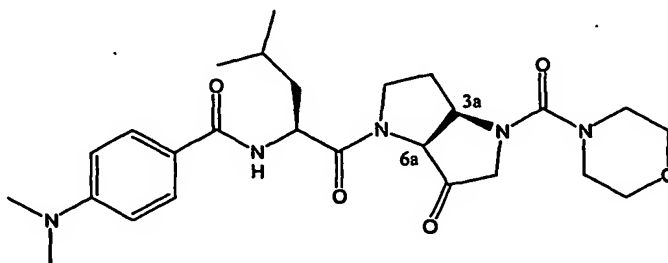


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HPLC Rt = 12.9-13.8 mins (> 75%), HPLC-MS 485.2 [M + H]⁺, 503.3 [M + H + H₂O]⁺, 991.5 [2M + Na]⁺.

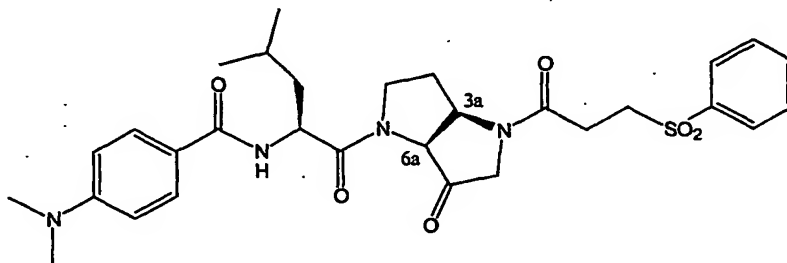
-373-

EXAMPLE 142. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(morpholine-4-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



HPLC Rt = 9.82 mins (> 85%), HPLC-MS 500.2 [M + H]⁺.

EXAMPLE 143. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(3-Benzenesulfonyl-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

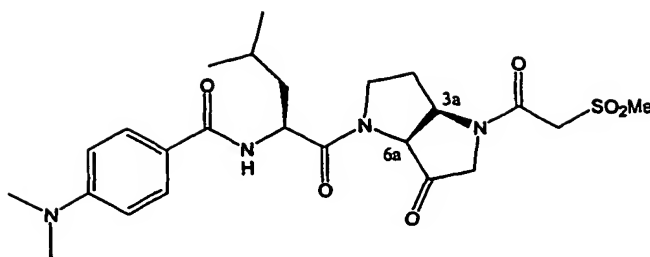


15 HPLC Rt = 12.27 mins (> 90%), HPLC-MS 583.2 [M + H]⁺.

EXAMPLE 144. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(2-methanesulfonyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

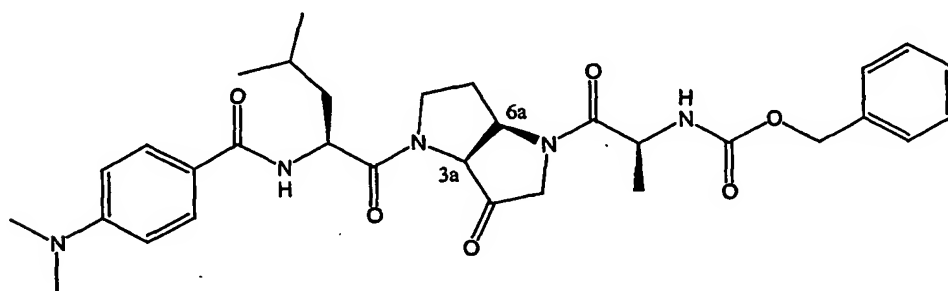
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-374-



HPLC Rt = 8.00 mins (> 50%), HPLC-MS 507.1 [M + H]⁺.

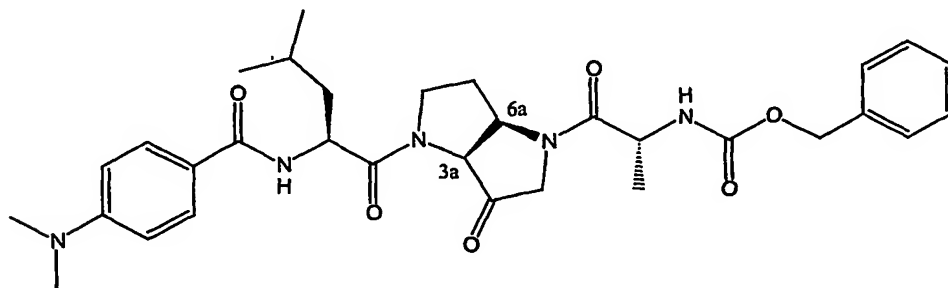
- 5 EXAMPLE 145. (3a*S*, 6a*R*)-((1*S*)-2-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid benzyl ester



10

HPLC Rt = 12.4-14.0 mins (> 85%), HPLC-MS 592.2 [M + H]⁺.

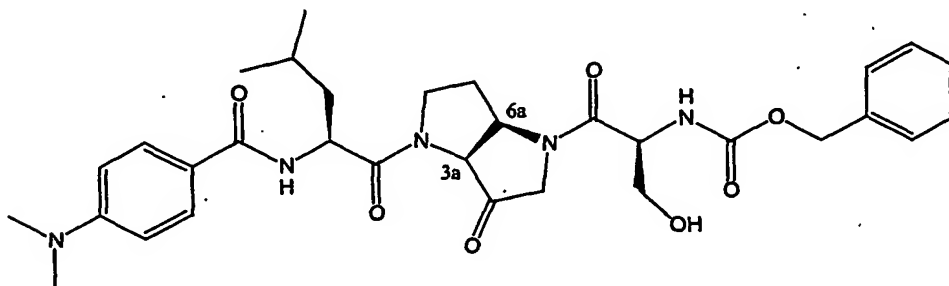
- 15 EXAMPLE 146. (3a*S*, 6a*R*)-((1*R*)-2-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl}-1-methyl-2-oxo-ethyl)-carbamic acid benzyl ester



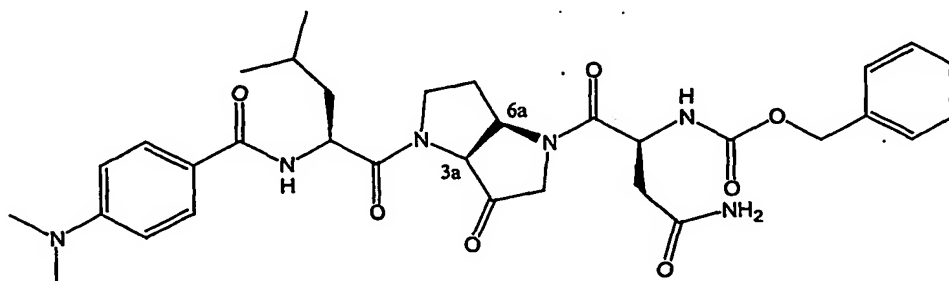
-375-

HPLC Rt = 12.5-13.9 mins (> 75%), HPLC-MS 592.2 [M + H]⁺.

EXAMPLE 147. (3a*S*, 6a*R*)-((1*S*)-2-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl}-1-hydroxymethyl-2-oxo-ethyl)-carbamic acid benzyl ester

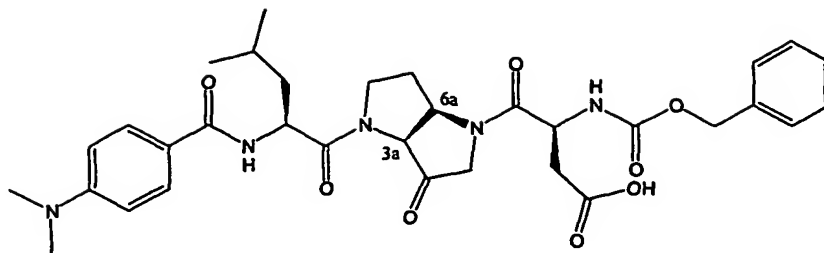
HPLC Rt = 11.8-13.3 mins (> 80%), HPLC-MS 608.3 [M + H]⁺.

EXAMPLE 148. (3a*S*, 6a*R*)-((1*S*)-1-Carbamoylmethyl-2-{4-[(2*S*)-2-(4-dimethylaminobenzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl}-2-oxo-ethyl)-carbamic acid benzyl ester

HPLC Rt = 11.4-13.2 mins (> 75%), HPLC-MS 635.2 [M + H]⁺.

EXAMPLE 149. (3a*S*, 6a*R*)-(3*S*)-3-Benzoyloxycarbonylamino-4-{4-[(2*S*)-2-(4-dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl}-4-oxo-butyric acid

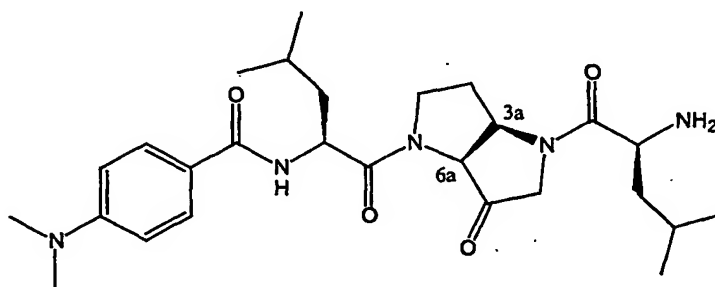
-376-



HPLC Rt = 12.1-13.5 mins (> 85%), HPLC-MS 636.2 [M + H]⁺, 654.3 [M + H + H₂O]⁺.

5

EXAMPLE 150. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

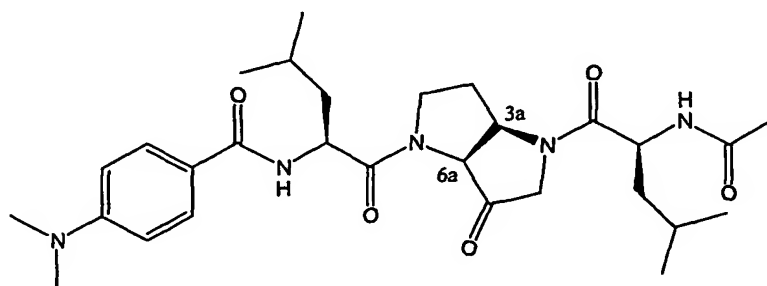


10

HPLC Rt = 11.00 mins (> 90%), HPLC-MS 500.2 [M + H]⁺, 999.5 [2M + H]⁺.

EXAMPLE 151. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

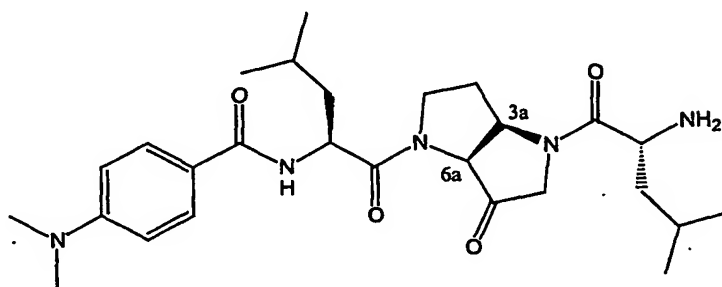
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-377-

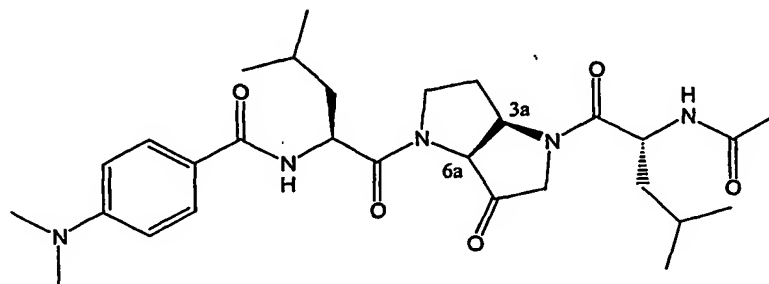
HPLC Rt = 11.5-13.0 mins (> 90%), HPLC-MS 542.2 [M + H]⁺.

EXAMPLE 152. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*R*)-2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



HPLC Rt = 8.9-10.8 mins (> 90%), HPLC-MS 500.2 [M + H]⁺, 999.5 [2M + H]⁺.

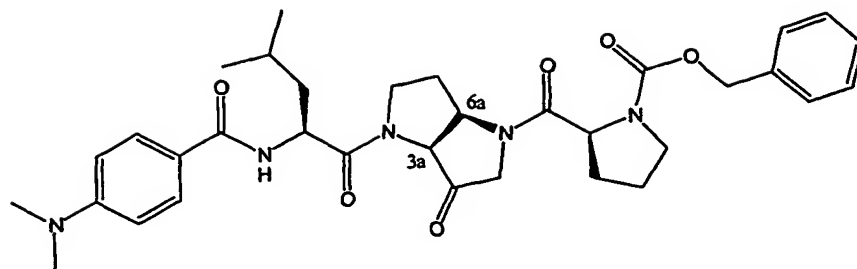
EXAMPLE 153. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*R*)-2-Acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



HPLC Rt = 10.4-12.2 mins (> 85%), HPLC-MS 542.3 [M + H]⁺.

EXAMPLE 154. (3a*S*, 6a*R*)-(2*S*)-2-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-pyrrolidine-1-carboxylic acid benzyl ester

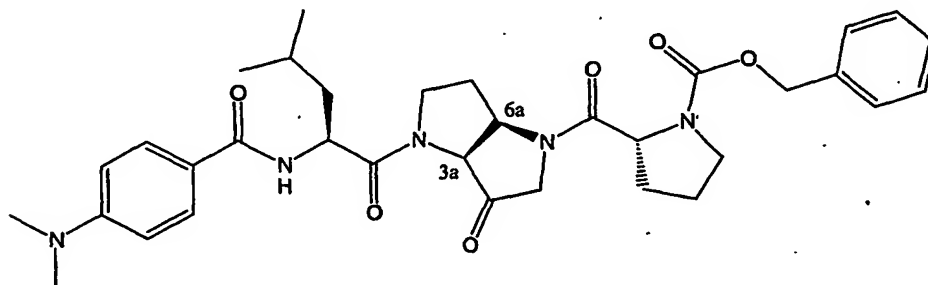
-378-



HPLC Rt = 13.2-14.3 mins (> 90%), HPLC-MS 618.2 [M + H]⁺.

5

EXAMPLE 155. (3aS, 6aR)-(2R)-2-{4-[(2S)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl}-pyrrolidine-1-carboxylic acid benzyl ester

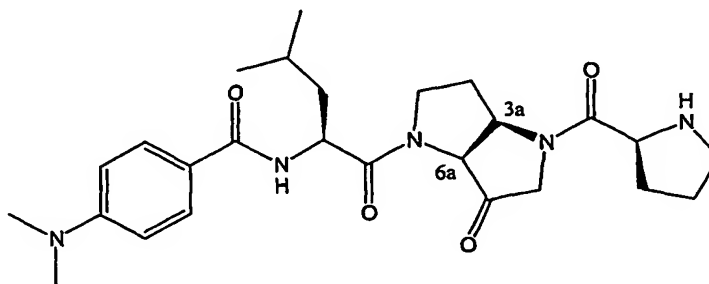


10

HPLC Rt = 13.2-14.2 mins (> 90%), HPLC-MS 618.2 [M + H]⁺.

EXAMPLE 156. (3aR, 6aS)-4-Dimethylamino-N-[(1S)-3-methyl-1-[6-oxo-4-((2S)-pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl]-benzamide

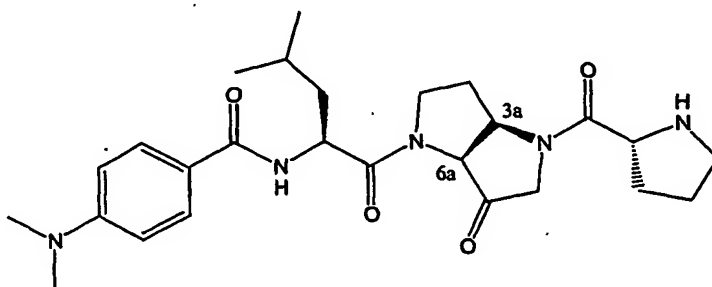
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-379-

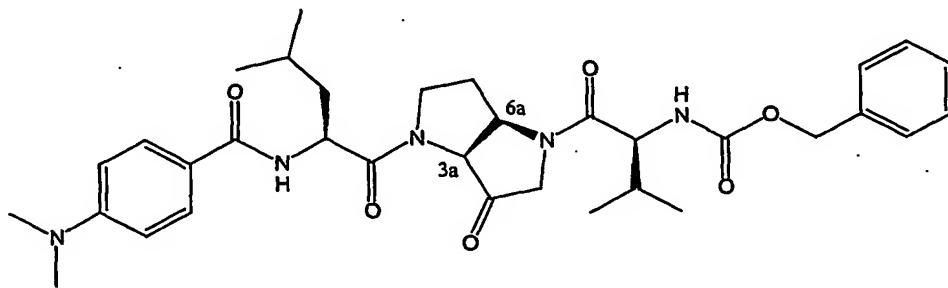
HPLC Rt = 8.82 mins (> 85%), HPLC-MS 484.2 [M + H]⁺, 967.4 [2M + H]⁺.

5 EXAMPLE 157. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-((2*R*)-pyrrolidine-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



10 HPLC Rt = 7.3-9.1 mins (> 85%), HPLC-MS 484.2 [M + H]⁺, 502.2 [M + H + H₂O]⁺, 985.4 [2M + H + H₂O]⁺.

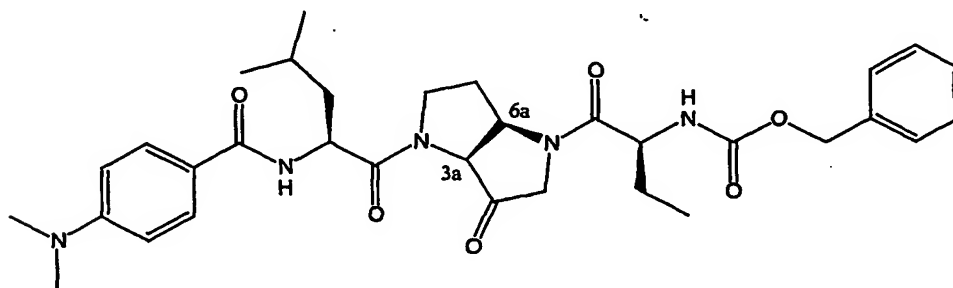
15 EXAMPLE 158. (3a*S*, 6a*R*)-((1*S*)-1-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-2-methyl-propyl)-carbamic acid benzyl ester



HPLC Rt = 15.18 mins (> 85%), HPLC-MS 620.3 [M + H]⁺.

-380-

EXAMPLE 159. (3a*S*, 6a*R*)-((1*S*)-1-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-propyl)-carbamic acid benzyl ester

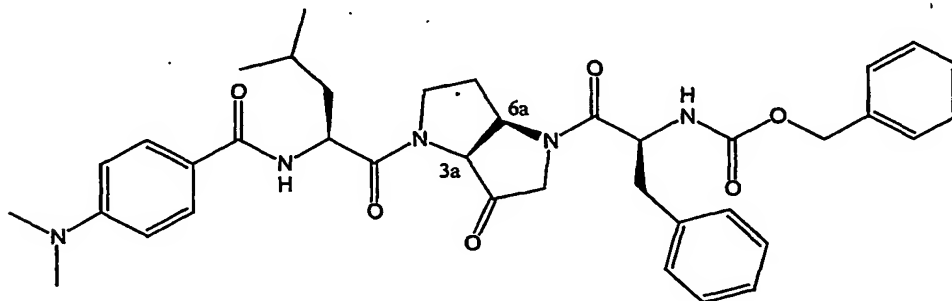


5

HPLC R_t = 14.22 mins (> 85%), HPLC-MS 606.2 $[M + H]^+$.

EXAMPLE 160. (3a*S*, 6a*R*)-((1*S*)-1-Benzyl-2-{4-[(2*S*)-2-(4-dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl}-2-oxo-ethyl)-carbamic acid benzyl ester

10



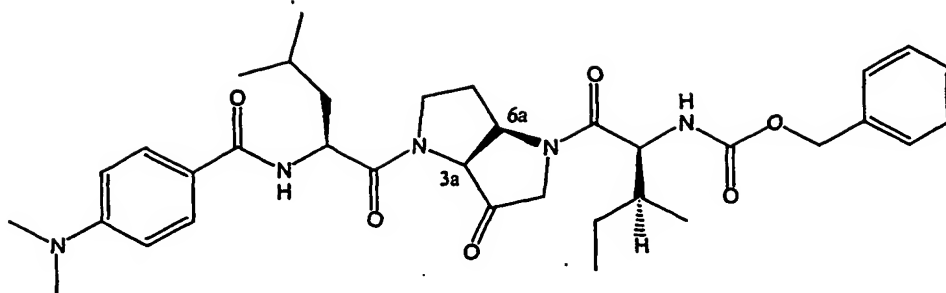
15

HPLC R_t = 16.23 mins (> 80%), HPLC-MS 668.2 $[M + H]^+$.

EXAMPLE 161. (3a*S*, 6a*R*)-((1*S*, 2*S*)-1-{4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-2-methyl-butyl)-carbamic acid benzyl ester

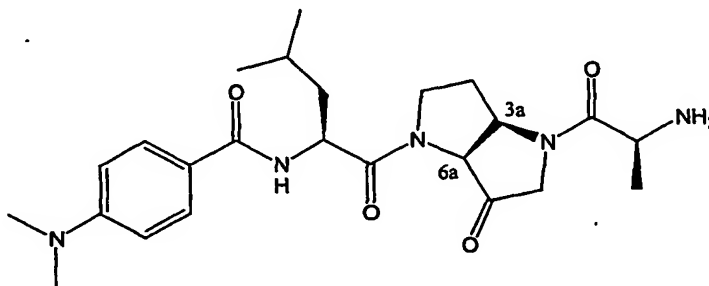
20

-381-



HPLC Rt = 16.17 mins (> 90%), HPLC-MS 634.3 [M + H]⁺.

- 5 EXAMPLE 162. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Amino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

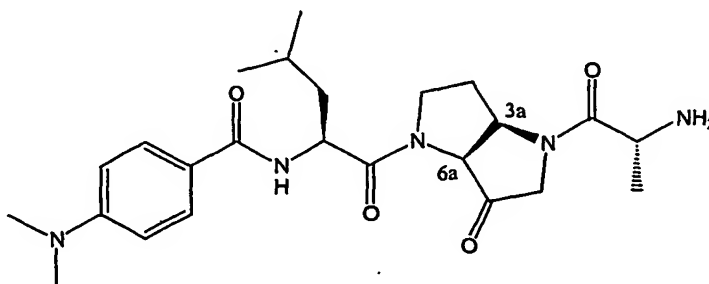


10

HPLC Rt = 8.01 mins (> 90%), HPLC-MS 458.2 [M + H]⁺, 937.4 [2M + Na]⁺.

15

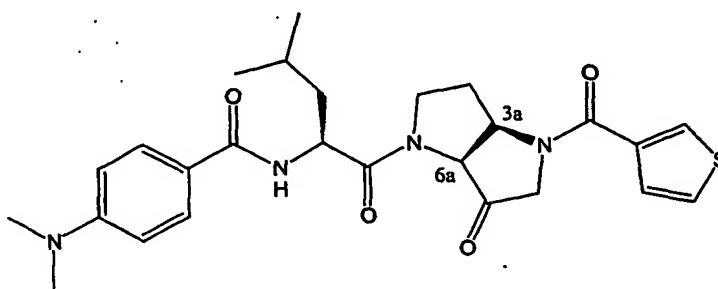
- EXAMPLE 163. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*R*)-2-Amino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



-382-

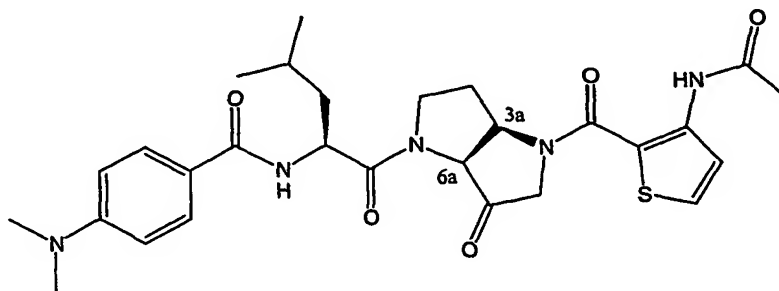
HPLC Rt = 6.9-8.3 mins (> 90%), HPLC-MS 458.2 [M + H]⁺, 937.4 [2M + Na]⁺.

EXAMPLE 164. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(thiophene-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



HPLC Rt = 11.0-12.0 mins (> 90%), HPLC-MS 497.2 [M + H]⁺, 515.2 [M + H + H₂O]⁺.

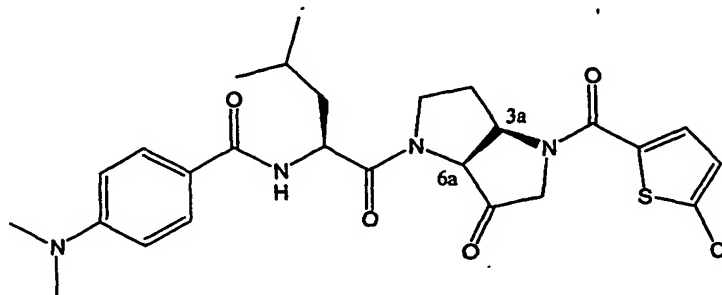
EXAMPLE 165. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(3-Acetylamino-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



HPLC Rt = 10.94 mins (> 80%), HPLC-MS 554.2 [M + H]⁺, 572.2 [M + H + H₂O]⁺.

-383-

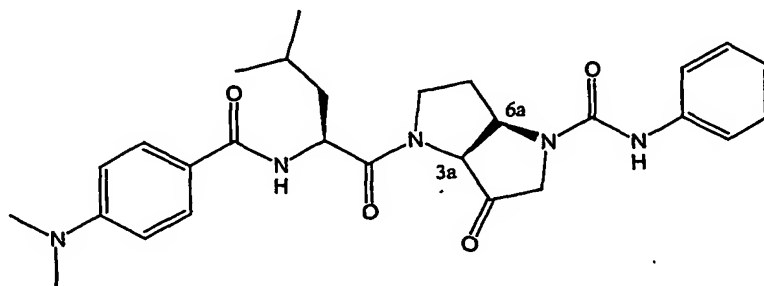
EXAMPLE 166. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(5-Chloro-thiophene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



5

HPLC R_t = 13.83 mins (> 95%), HPLC-MS 531.1 / 533.1 $[M + H]^+$, 549.1 / 551.1 $[M + H + H_2O]^+$.

10 EXAMPLE 167. (3a*S*, 6a*R*)-4-[(2*S*)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide



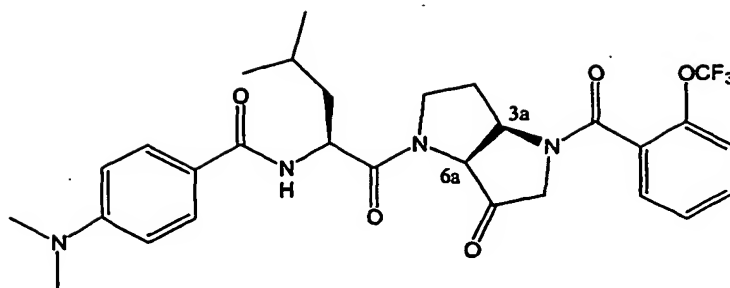
15

HPLC R_t = 11.4-12.1 mins (> 95%), HPLC-MS 506.2 $[M + H]^+$.

EXAMPLE 168. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(2-trifluoromethoxy-benzoyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

20

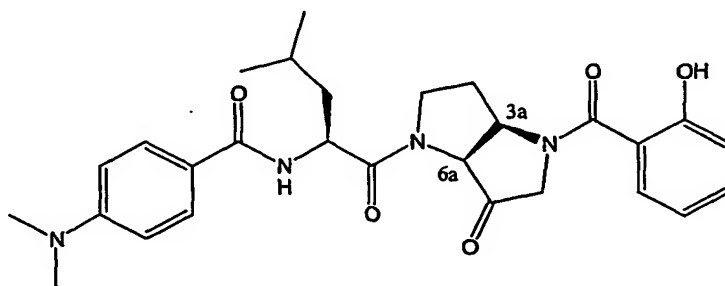
-384-



HPLC Rt = 14.42 mins (> 85%), HPLC-MS 575.2 [M + H]⁺, 593.2 [M + H + H₂O]⁺.

5

EXAMPLE 169. (3aR, 6aS)-4-Dimethylamino-N-[(1S)-1-[4-(2-hydroxy-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl]-benzamide

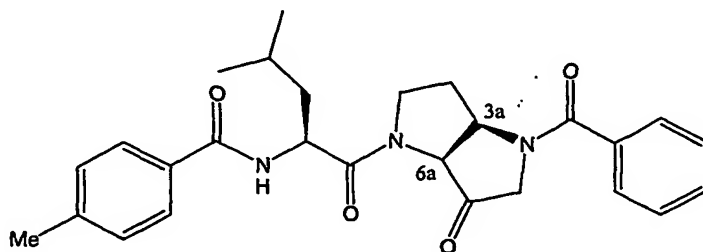


10

HPLC Rt = 7.77 mins (> 50%), HPLC-MS 507.2 [M + H]⁺.

EXAMPLE 170. (3aR, 6aS)-N-[(1S)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl)-3-methyl-butyl]-4-methyl-benzamide

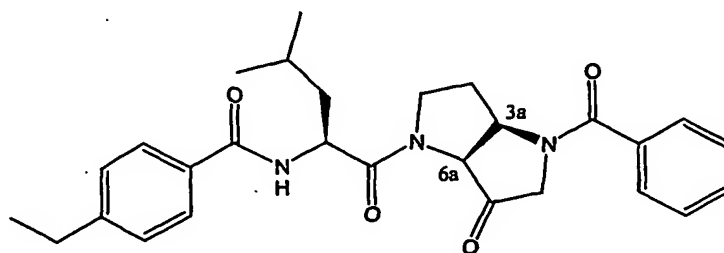
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HPLC Rt = 14.35 mins (> 90%), HPLC-MS 462.2 [M + H]⁺, 945.3 [2M + Na]⁺.

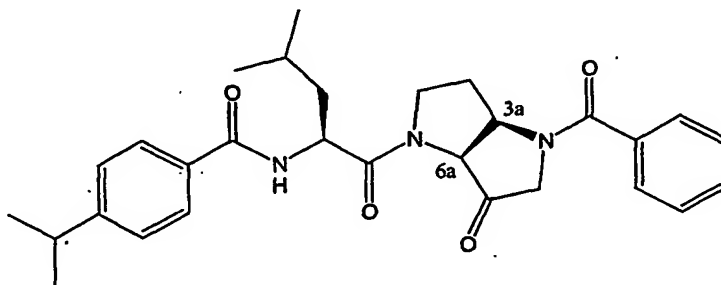
-385-

EXAMPLE 171. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrole-1-carbonyl)-3-methyl-butyl]-4-ethyl-benzamide



HPLC Rt = 15.40 mins (> 90%), HPLC-MS 476.2 [M + H]⁺, 973.4 [2M + Na]⁺.

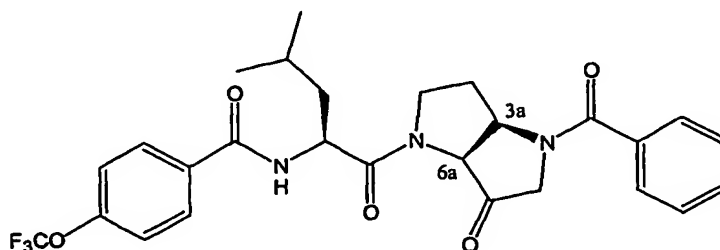
EXAMPLE 172. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrole-1-carbonyl)-3-methyl-butyl]-4-isopropyl-benzamide



HPLC Rt = 16.41 mins (> 85%), HPLC-MS 490.2 [M + H]⁺.

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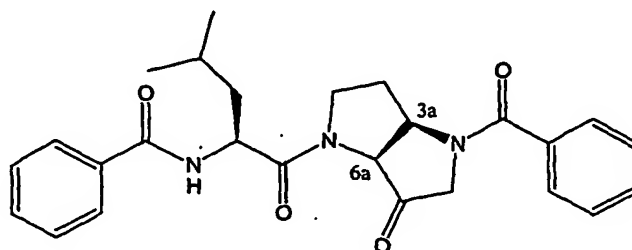
EXAMPLE 173. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrole-1-carbonyl)-3-methyl-butyl]-4-trifluoromethoxy-benzamide



-386-

HPLC Rt = 16.44 mins (> 90%), HPLC-MS 532.1 [M + H]⁺.

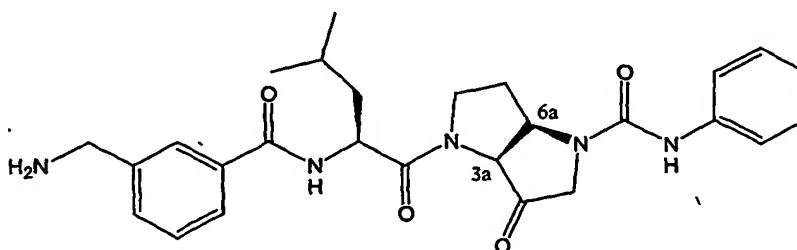
EXAMPLE 174. (3aR, 6aS)-N-[(1S)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-
5 b] pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide



HPLC Rt = 13.30 mins (> 90%), HPLC-MS 448.2 [M + H]⁺, 470.1 [M + Na]⁺,
10 917.2 [2M + Na]⁺.

EXAMPLE 175. (3aS, 6aR)-4-[(2S)-2-(3-Aminomethyl-benzoylamino)-4-methyl-
pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carboxylic acid
phenylamide

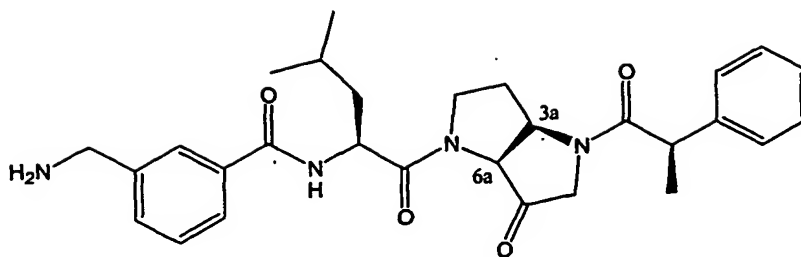
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HPLC Rt = 10.69 mins (> 95%), HPLC-MS 492.2 [M + H]⁺, 983.4 [2M + H]⁺.

20 EXAMPLE 176. (3aR, 6aS)-3-Aminomethyl-N-[(1S)-3-methyl-1-[6-oxo-4-((2R)-
2-phenyl-propionyl)-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl]-
benzamide

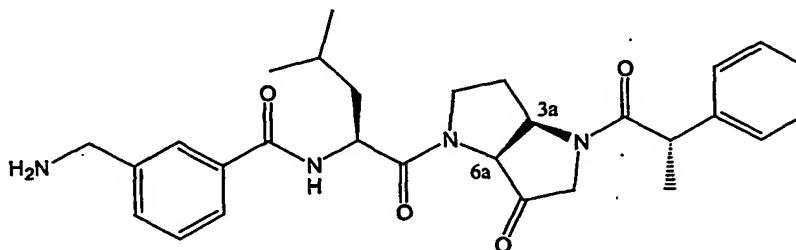
-387-



HPLC Rt = 12.2-13.8 mins (> 90%), HPLC-MS 505.2 [M + H]⁺, 523.2 [M + H + H₂O]⁺.

5

EXAMPLE 177. (3aR, 6aS)-3-Aminomethyl-N-((1S)-3-methyl-1-[6-oxo-4-((2S)-2-phenyl-propionyl)-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl)-benzamide

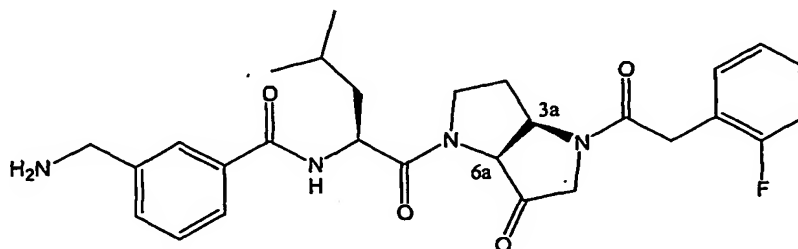


10

HPLC Rt = 11.9-13.5 mins (> 85%), HPLC-MS 505.2 [M + H]⁺.

EXAMPLE 178. (3aR, 6aS)-3-Aminomethyl-N-((1S)-1-{4-[2-(2-fluoro-phenyl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl}-3-methyl-butyl)-benzamide

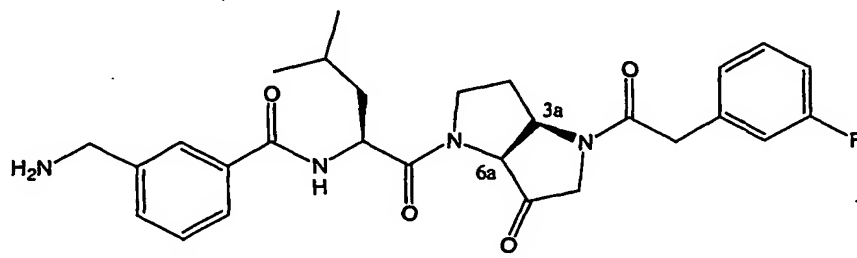
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-388-

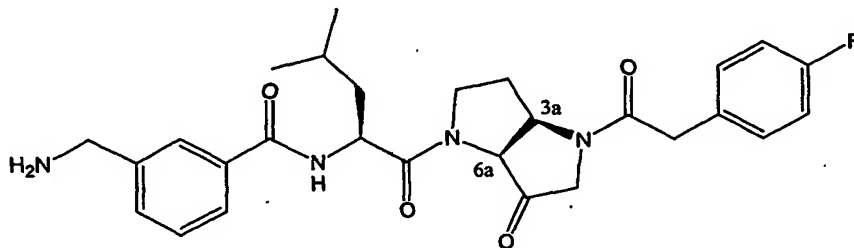
HPLC Rt = 11.65 mins (> 90%), HPLC-MS 509.2 [M + H]⁺.

EXAMPLE 179. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-((1*S*)-1-{4-[2-(3-fluoro-phenyl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-benzamide



HPLC Rt = 11.70 mins (> 95%), HPLC-MS 509.2 [M + H]⁺.

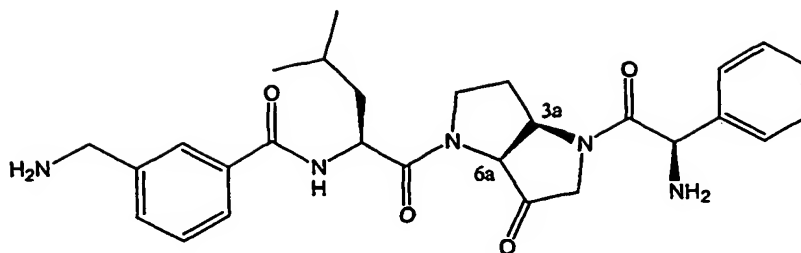
EXAMPLE 180. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-((1*S*)-1-{4-[2-(4-fluoro-phenyl)-acetyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl)-benzamide



HPLC Rt = 11.74 mins (> 95%), HPLC-MS 509.2 [M + H]⁺.

EXAMPLE 181. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-{(1*S*)-1-[4-((2*R*)-2-amino-2-phenyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

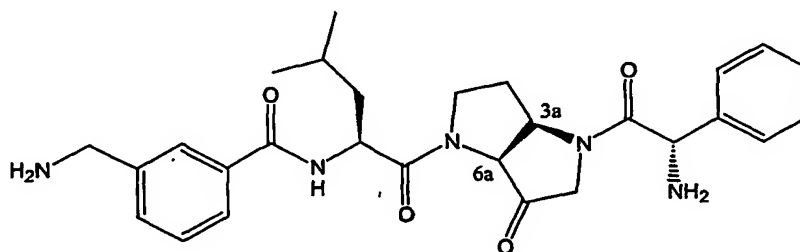
-389-



HPLC Rt = 8.93 mins (> 50%), HPLC-MS 506.2 $[M + H]^+$, 524.2 $[M + H + H_2O]^+$.

5

EXAMPLE 182. (3aR, 6aS)-3-Aminomethyl-N-{(1S)-1-[4-((2S)-2-amino-2-phenyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

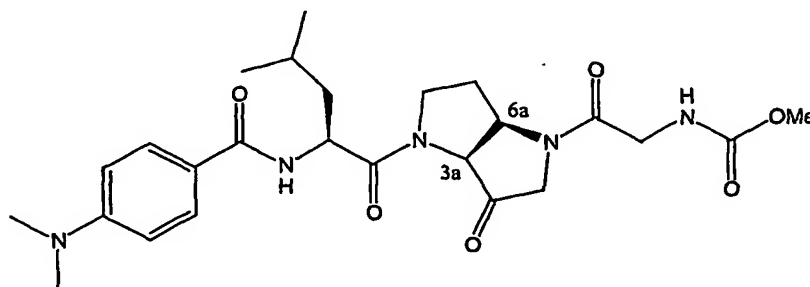


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HPLC Rt = 7.2-9.3 mins (> 60%), HPLC-MS 506.2 $[M + H]^+$, 524.2 $[M + H + H_2O]^+$.

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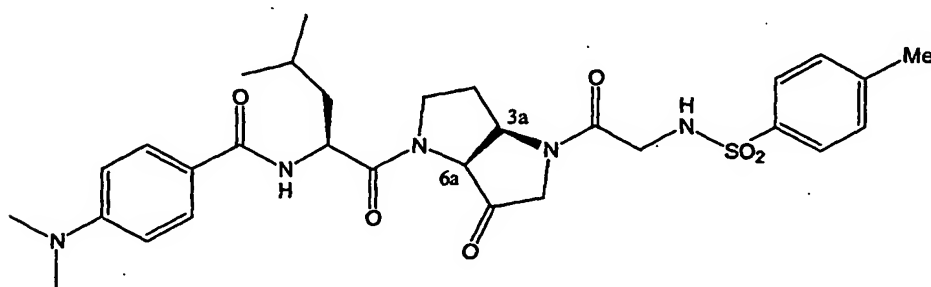
EXAMPLE 183. (3aS, 6aR)-(2-{4-[(2S)-2-(4-Dimethylamino-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl}-2-oxo-ethyl)-carbamic acid methyl ester



-390-

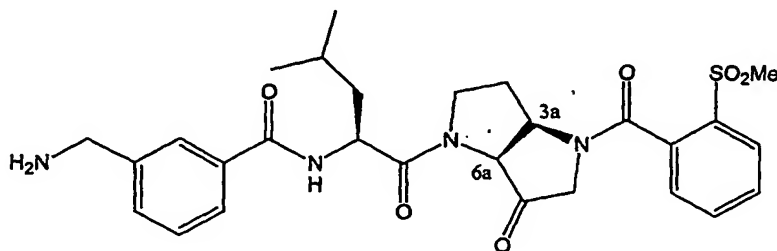
HPLC Rt = 7.96 mins (> 95%), HPLC-MS 502.2 [M + H]⁺.

EXAMPLE 184. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-((1*S*)-3-methyl-1-{6-oxo-4-[2-(toluene-4-sulfonylamino)-acetyl]-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-butyl)-benzamide



HPLC Rt = 13.40 mins (> 90%), HPLC-MS 598.2 [M + H]⁺.

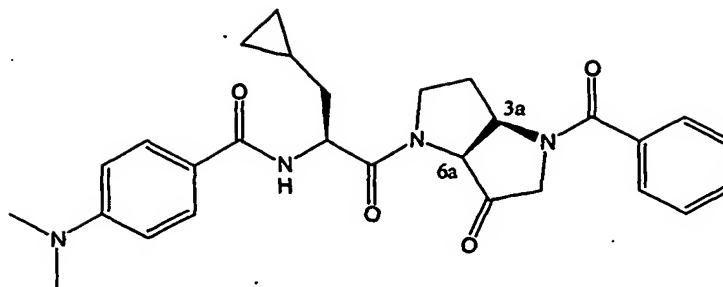
EXAMPLE 185. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-{(1*S*)-1-[4-(2-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide



HPLC Rt = 9.4-10.4 mins (> 85%), HPLC-MS 555.2 [M + H]⁺, 573.2 [M + H + H₂O]⁺.

EXAMPLE 186. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-cyclopropylmethyl-2-oxo-ethyl]-4-dimethylamino-benzamide

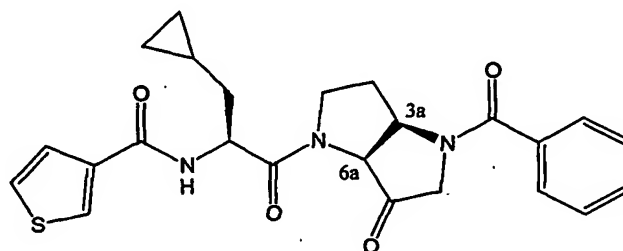
-391-



HPLC R_t = 11.0-13.0 mins (> 85%), HPLC-MS $[489.2 \text{ M} + \text{H}]^+$, $507.2 [\text{M} + \text{H} + \text{H}_2\text{O}]^+$.

5

EXAMPLE 187. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid [(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-cyclopropylmethyl-2-oxo-ethyl]-amide

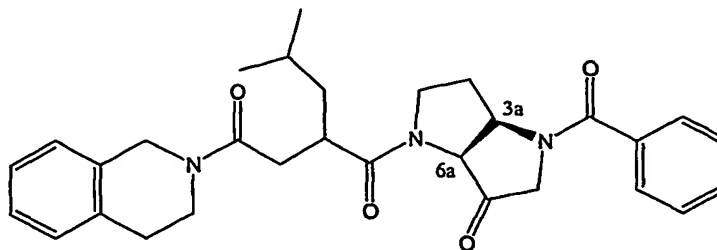


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HPLC R_t = 12.10 mins (> 80%), HPLC-MS $452.1 [\text{M} + \text{H}]^+$, $925.2 [2\text{M} + \text{Na}]^+$.

EXAMPLE 188. (3a*R*, 6a*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-4-(3,4-dihydro-1*H*-isoquinolin-2-yl)-2-isobutyl-butane-1,4-dione

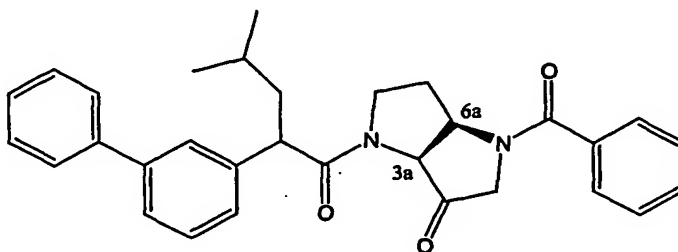
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-392-

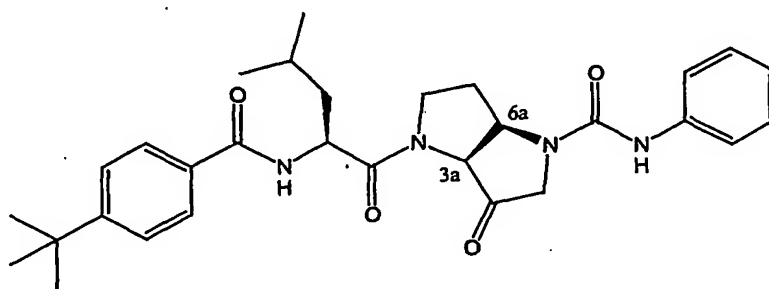
HPLC Rt = 15.1-16.5 mins (> 80%), HPLC-MS 502.1 [M + H]⁺, 520.2 [M + H + H₂O]⁺.

5 EXAMPLE 189. (3a*S*, 6a*R*)-1-Benzoyl-4-(2-biphenyl-3-yl-4-methyl-pentanoyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-3-one



10 HPLC Rt = 18.1-20.1 mins (> 80%), HPLC-MS 481.2 [M + H]⁺, 499.2 [M + H + H₂O]⁺, 983.3 [2M + Na]⁺.

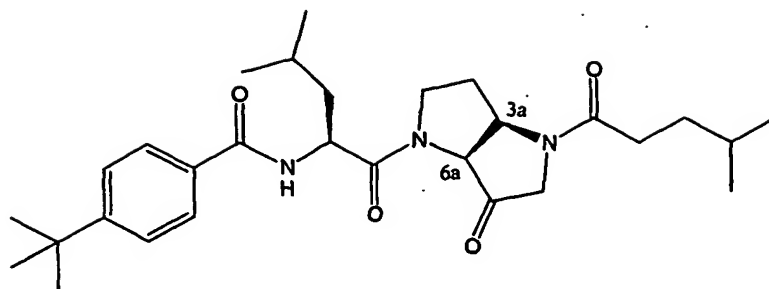
EXAMPLE 190. (3a*S*, 6a*R*)-4-[(2*S*)-2-(4-*tert*-Butyl-benzoylamino)-4-methyl-pentanoyl]-3-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid phenylamide



HPLC Rt = 16.9-18.4 mins (> 85%), HPLC-MS 519.2 [M + H]⁺.

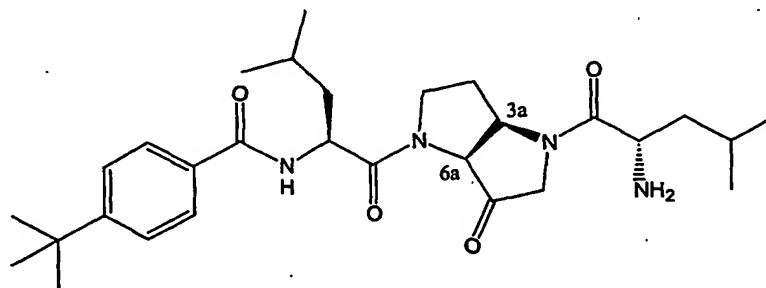
20 EXAMPLE 191. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-3-methyl-1-[4-(4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

-393-



HPLC Rt = 16.3-17.5 mins (> 85%), HPLC-MS 498.2 [M + H]⁺.

- 5 EXAMPLE 192. (3aR, 6aS)-N-((1S)-1-[4-((2S)-2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-4-tert-butyl-benzamide

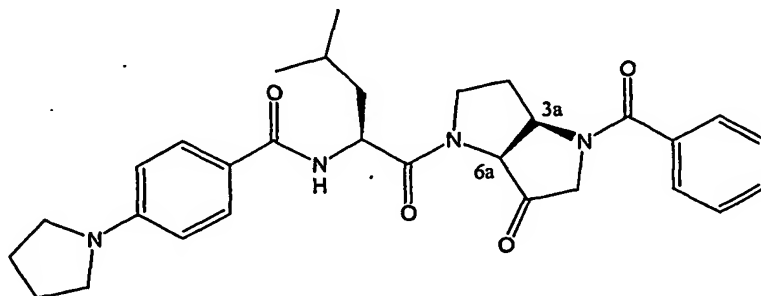


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HPLC Rt = 16.19 mins (> 90%), HPLC-MS 513.3 [M + H]⁺.

- EXAMPLE 193. (3aR, 6aS)-N-[(1S)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b] pyrrole-1-carbonyl)-3-methyl-butyl]-4-pyrrolidin-1-yl-benzamide

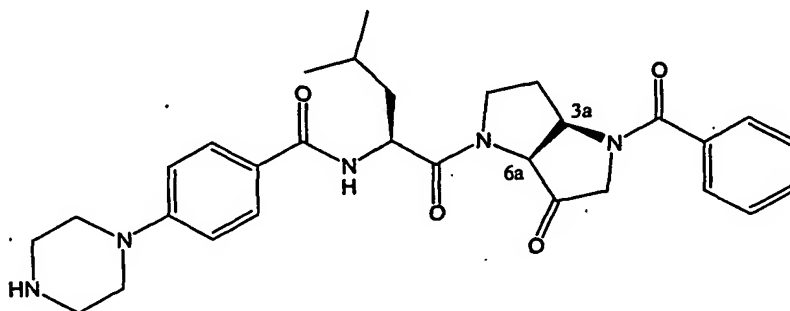
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-394-

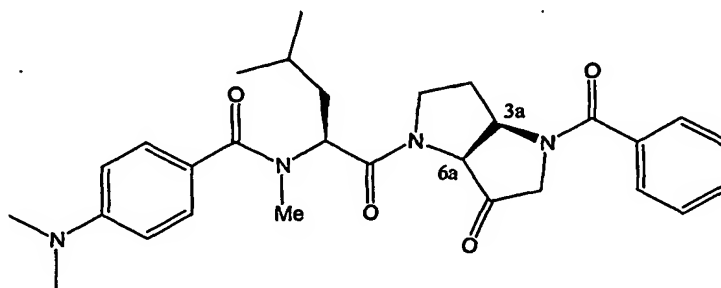
HPLC Rt = 17.45 mins (> 85%), HPLC-MS 517.1 [M + H]⁺, 535.2 [M + H + H₂O]⁺.

EXAMPLE 194. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-
5 b] pyrrole-1-carbonyl)-3-methyl-butyl]-4-piperazin-1-yl-benzamide



HPLC Rt = 11.50 mins (> 95%), HPLC-MS 532.1 [M + H]⁺, 550.2 [M + H + H₂O]⁺.

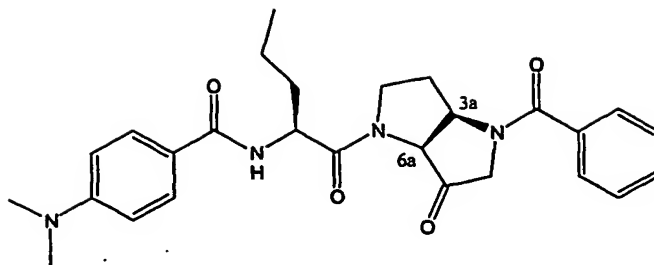
EXAMPLE 195. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-
b] pyrrole-1-carbonyl)-3-methyl-butyl]-4-dimethylamino-*N*-methyl-benzamide



HPLC Rt = 18.29 mins (> 50%), HPLC-MS 505.1 [M + H]⁺.

EXAMPLE 196. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-
20 b] pyrrole-1-carbonyl)-butyl]-4-dimethylamino-benzamide

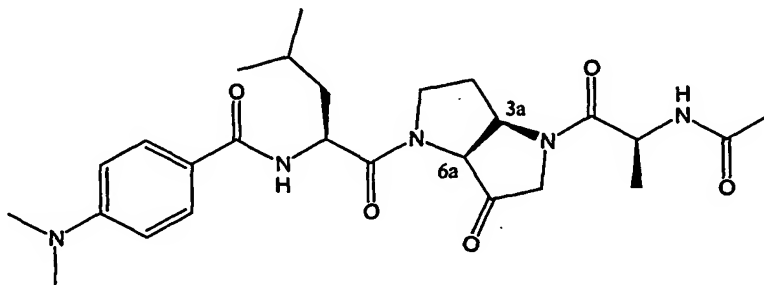
-395-



HPLC Rt = 11.09 mins (> 80%), HPLC-MS 477.1 [M + H]⁺, 495.1 [M + H + H₂O]⁺.

5

EXAMPLE 197. (3aR, 6aS)-N-{(1S)-1-[4-((2S)-2-Acetyl-amino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

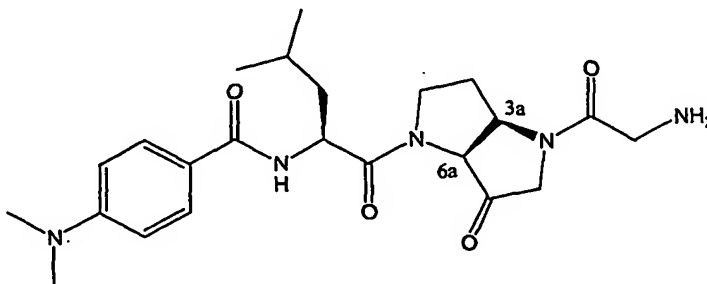


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HPLC Rt = 9.06 mins (> 90%), HPLC-MS 500.1 [M + H]⁺, 518.2 [M + H + H₂O]⁺.

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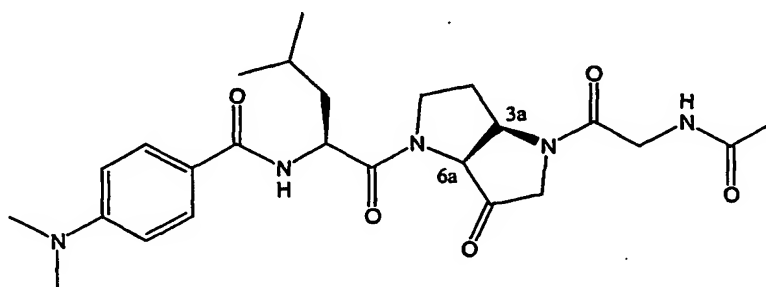
EXAMPLE 198. (3aR, 6aS)-N-{(1S)-1-[4-(2-Amino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



-396-

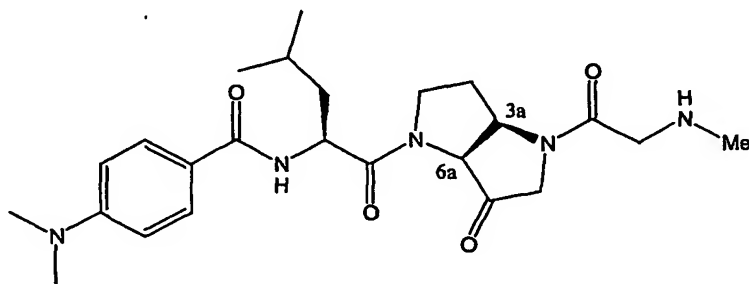
HPLC Rt = 7.93 mins (> 90%), HPLC-MS 444.1 [M + H]⁺.

EXAMPLE 199. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(2-Acetylamino-acetyl)-6-oxo-
5 hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-
benzamide



10 HPLC Rt = 8.1 mins (> 90%), HPLC-MS 486.1 [M + H]⁺.

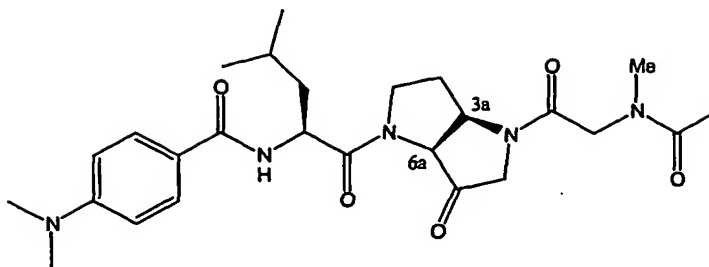
EXAMPLE 200. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(2-
methylamino-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-
15 benzamide



HPLC Rt = 7.89 mins (> 90%), HPLC-MS 458.2 [M + H]⁺.

20 EXAMPLE 201. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-[2-(Acetyl-methyl-amino)-acetyl]-6-
oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-
dimethylamino-benzamide

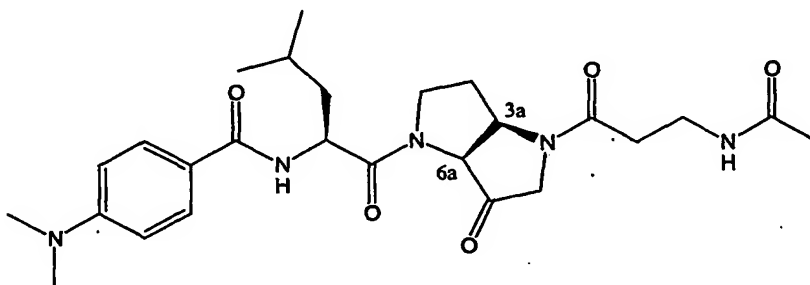
-397-



HPLC Rt = 8.89 mins (> 90%), HPLC-MS 500.2 [M + H]⁺.

5

EXAMPLE 202. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(3-Acetyl-amino-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethyl-amino-benzamide

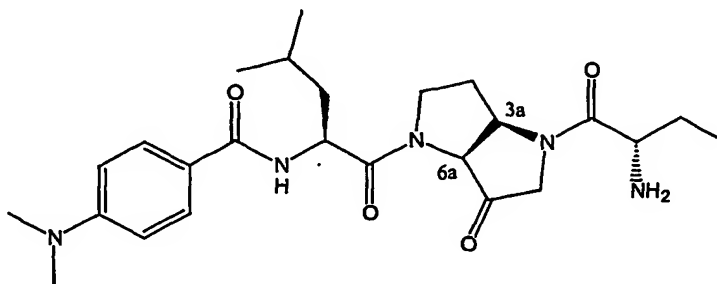


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HPLC Rt = 8.57 mins (> 90%), HPLC-MS 500.1 [M + H]⁺.

EXAMPLE 203. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Amino-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethyl-amino-benzamide

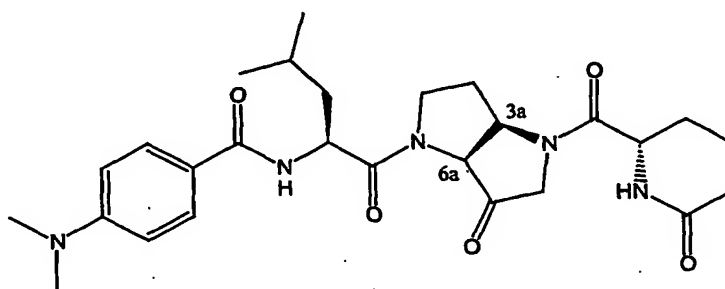
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-398-

HPLC Rt = 9.29 mins (> 90%), HPLC-MS 472.2 [M + H]⁺.

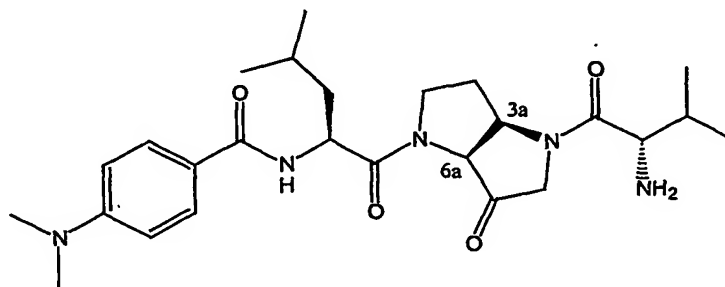
5 EXAMPLE 204. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Acetylamino-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



10 HPLC Rt = 10.45 mins (> 90%), HPLC-MS 514.2 [M + H]⁺.

EXAMPLE 205. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Amino-3-methyl-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

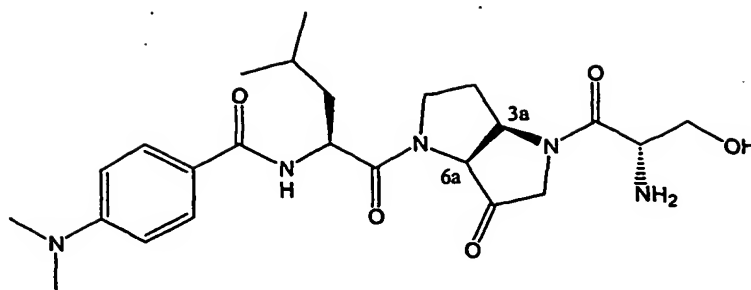
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HPLC Rt = 9.92 mins (> 90%), HPLC-MS 486.2 [M + H]⁺.

20 EXAMPLE 206. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Amino-3-hydroxy-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

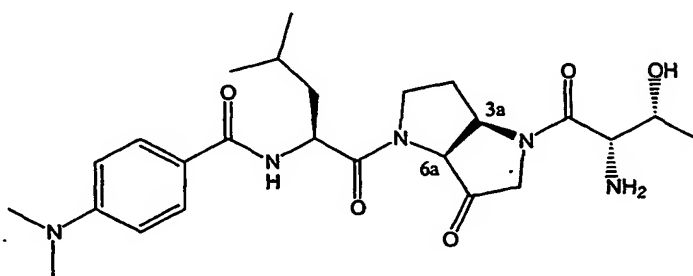
-399-



HPLC Rt = 7.56 mins (> 90%), HPLC-MS 474.1 $[M + H]^+$.

5

EXAMPLE 207. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*, 3*R*)-2-Amino-3-hydroxy-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

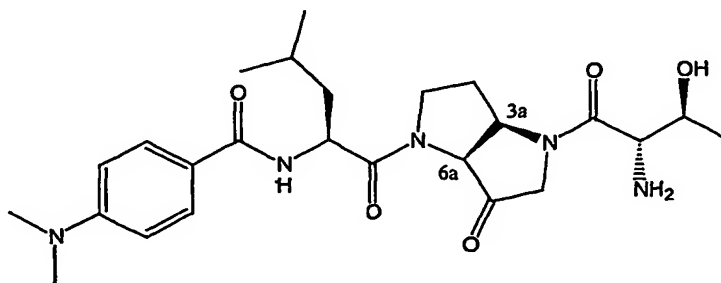


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HPLC Rt = 8.00 mins (> 80%), HPLC-MS 488.1 $[M + H]^+$.

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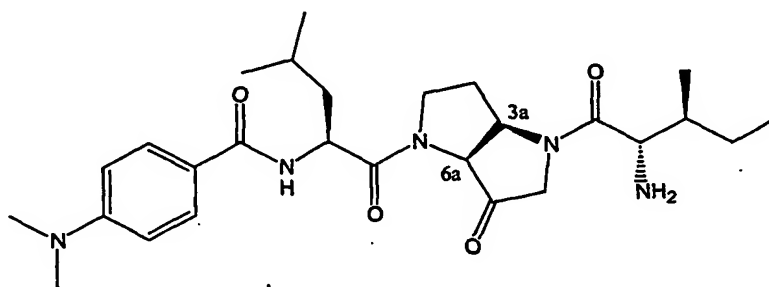
EXAMPLE 208. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*, 3*S*)-2-Amino-3-hydroxy-butyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



-400-

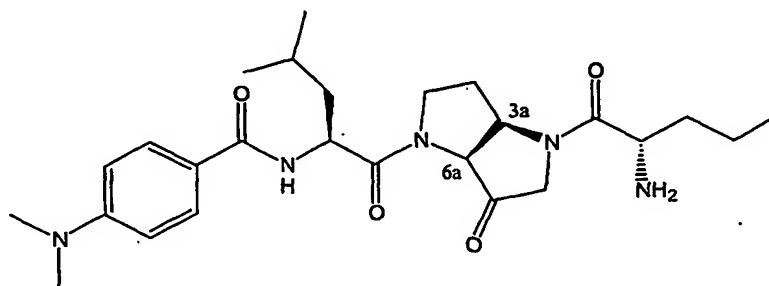
HPLC Rt = 8.13 mins (> 85%), HPLC-MS 488.1 [M + H]⁺.

EXAMPLE 209. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*, 3*S*)-2-Amino-3-methyl-
5 pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-
4-dimethylamino-benzamide



10 HPLC Rt = 10.97 mins (> 90%), HPLC-MS 500.2 [M + H]⁺.

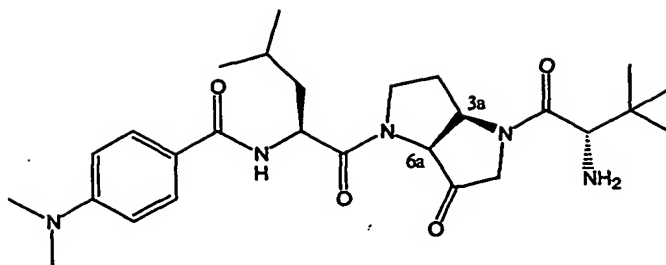
EXAMPLE 210. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Amino-pentanoyl)-6-oxo-
hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-,
15 benzamide



HPLC Rt = 10.32 mins (> 90%), HPLC-MS 486.2 [M + H]⁺.

20 EXAMPLE 211. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Amino-3,3-dimethyl-butyryl)-
6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-
dimethylamino-benzamide

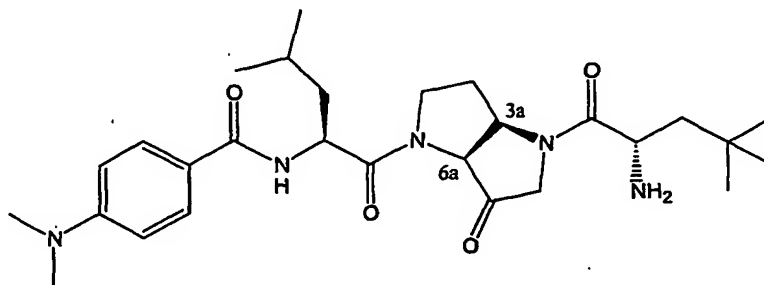
-401-



HPLC Rt = 11.14 mins (> 90%), HPLC-MS 500.2 [M + H]⁺.

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EXAMPLE 212. (3aR, 6aS)-N-((1S)-1-[4-((2S)-2-Amino-4,4-dimethylpentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-4-dimethylamino-benzamide

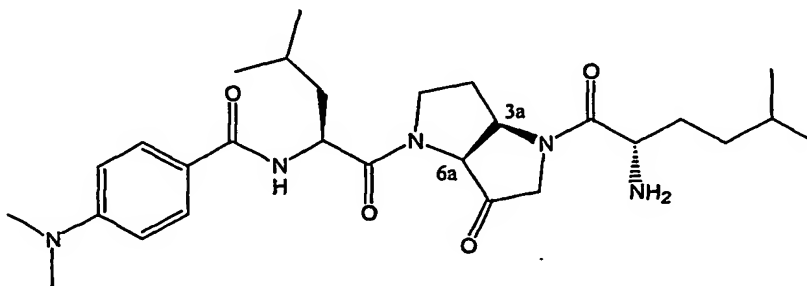


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HPLC Rt = 12.01 mins (> 90%), HPLC-MS 514.2 [M + H]⁺.

EXAMPLE 213. (3aR, 6aS)-N-((1S)-1-[4-((2S)-2-Amino-5-methyl-hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-4-dimethylamino-benzamide

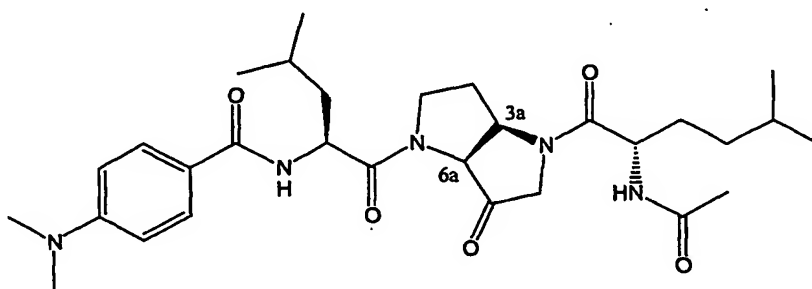
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-402-

HPLC Rt = 12.83 mins (> 95%), HPLC-MS 514.2 [M + H]⁺.

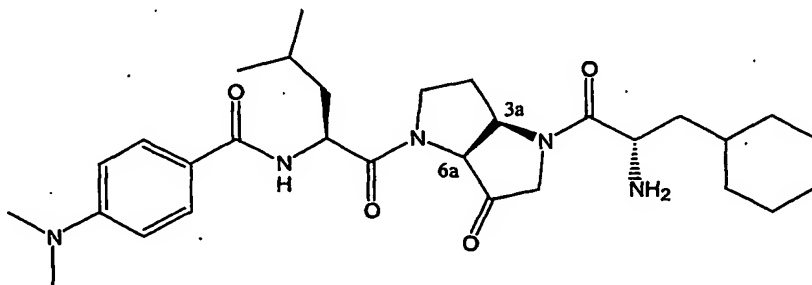
EXAMPLE 214. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Acetylamino-5-methyl-
5 hexanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-
4-dimethylamino-benzamide



10 HPLC Rt = 14.18 mins (> 95%), HPLC-MS 556.2 [M + H]⁺.

EXAMPLE 215. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Amino-3-cyclohexyl-
propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-
4-dimethylamino-benzamide

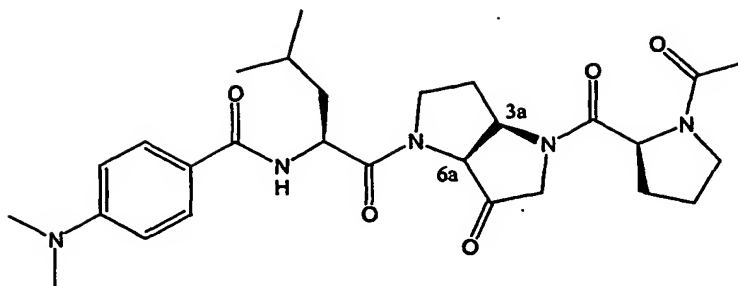
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HPLC Rt = 13.54 mins (> 95%), HPLC-MS 540.2 [M + H]⁺.

20 EXAMPLE 216. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-1-Acetyl-pyrrolidine-2-carbonyl)-
6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-
dimethylamino-benzamide

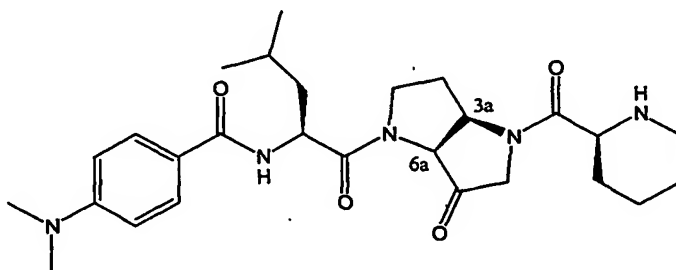
-403-



HPLC Rt = 9.88 mins (> 95%), HPLC-MS 526.2 [M + H]⁺.

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EXAMPLE 217. (3aR, 6aS)-4-Dimethylamino-N-((1S)-3-methyl-1-[6-oxo-4-((2S)-piperidine-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl)-benzamide

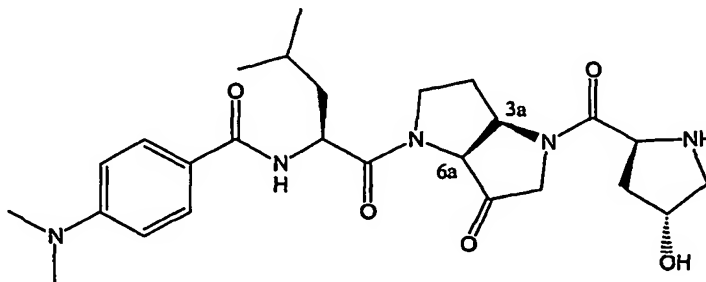


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HPLC Rt = 9.12 mins (> 90%), HPLC-MS 498.2 [M + H]⁺, 995.3 [2M + H]⁺.

EXAMPLE 218. (3aR, 6aS)-4-Dimethylamino-N-((1S)-1-[4-((2S, 4R)-4-hydroxy-pyrrolidine-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-3-methyl-butyl)-benzamide

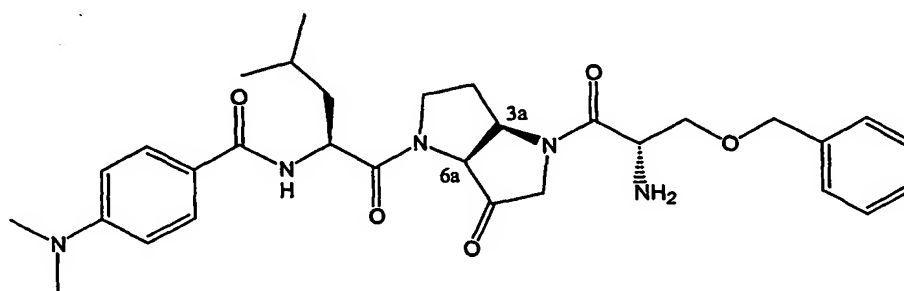
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-404-

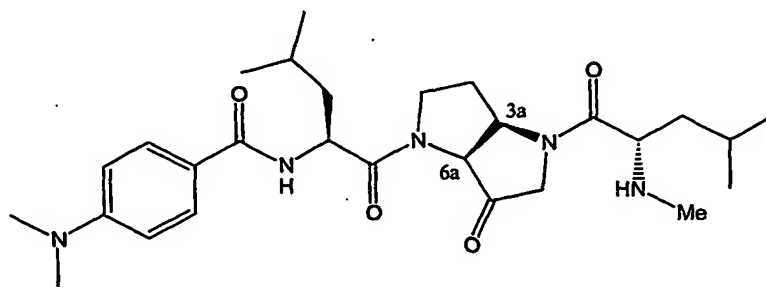
HPLC Rt = 8.00 mins (> 90%), HPLC-MS 500.2 [M + H]⁺, 999.3 [2M + H]⁺.

5 EXAMPLE 219. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Amino-3-benzyloxy-propionyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



10 HPLC Rt = 11.6-12.7 mins (> 85%), HPLC-MS 564.2 [M + H]⁺.

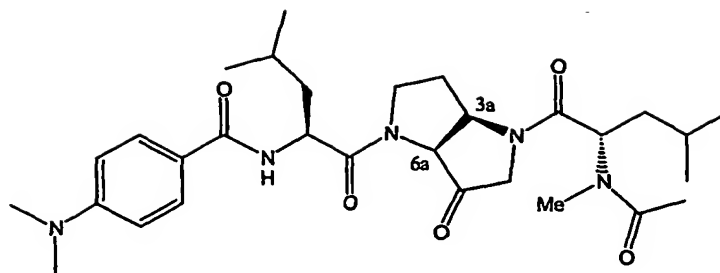
15 EXAMPLE 220. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-((2*S*)-4-methyl-2-methylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



HPLC Rt = 12.12 mins (> 90%), HPLC-MS 514.2 [M + H]⁺.

20 EXAMPLE 221. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-{4-[(2*S*)-2-(Acetyl-methyl-amino)-4-methyl-pentanoyl]-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl}-3-methyl-butyl}-4-dimethylamino-benzamide

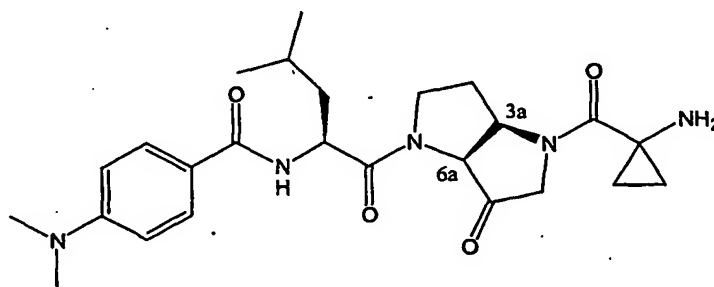
-405-



HPLC Rt = 13.37 mins (> 50%), HPLC-MS 556.2 [M + H]⁺.

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EXAMPLE 222. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(1-Amino-cyclopropanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

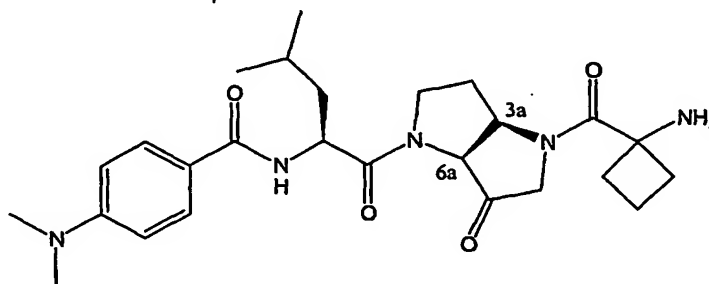


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HPLC Rt = 8.16 mins (> 50%), HPLC-MS 470.2 [M + H]⁺.

EXAMPLE 223. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(1-Amino-cyclobutanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

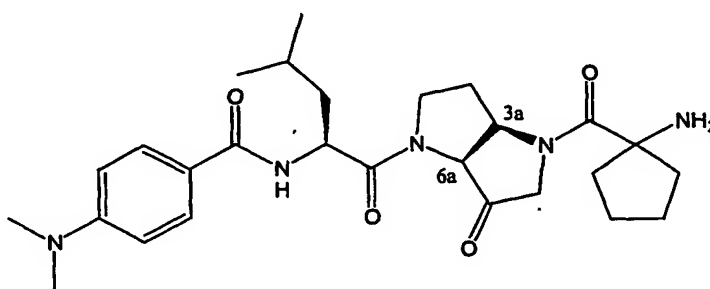
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-406-

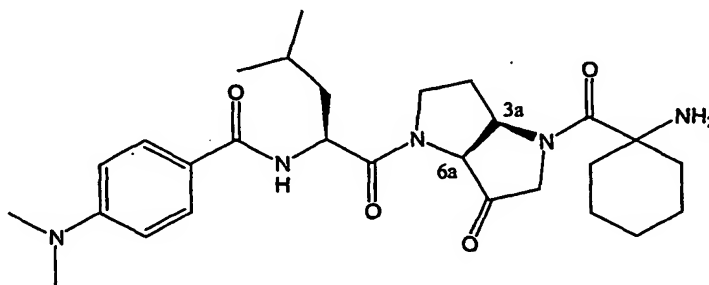
HPLC Rt = 8.4-8.9 mins (> 75%), HPLC-MS 484.2 [M + H]⁺.

EXAMPLE 224. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(1-Amino-cyclopentanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



HPLC Rt = 8.5-8.9 mins (> 40%), HPLC-MS 498.2 [M + H]⁺.

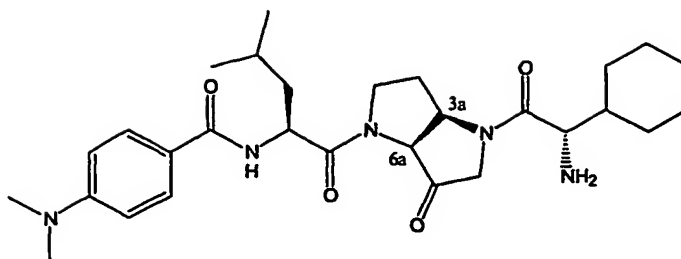
EXAMPLE 225. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(1-Amino-cyclohexanecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide



HPLC Rt = 9.1-9.5 mins (> 25%), HPLC-MS 529.9 [M + H + H₂O]⁺.

EXAMPLE 226. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Amino-2-cyclohexyl-acetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

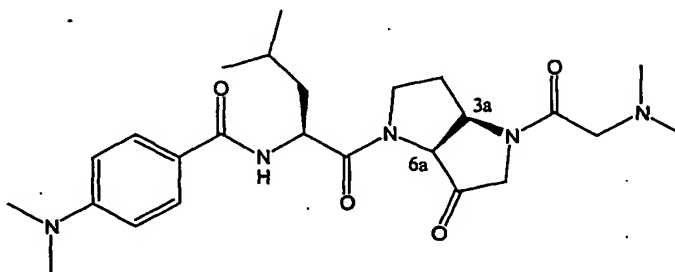
-407-



HPLC Rt = 12.17 mins (> 90%), HPLC-MS 526.2 [M + H]⁺.

5

EXAMPLE 227. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(2-dimethylaminoacetyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

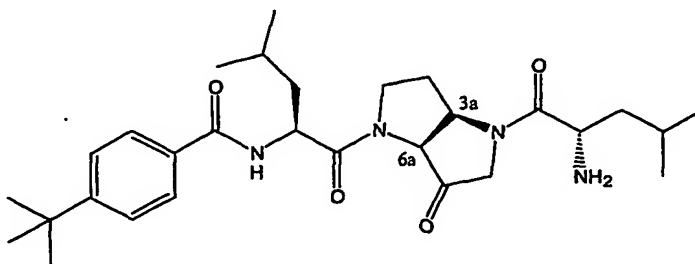


10

HPLC Rt = 7.7-8.1 mins (> 90%), HPLC-MS 472.2 [M + H]⁺, 490.2 [M + H + H₂O]⁺.

15

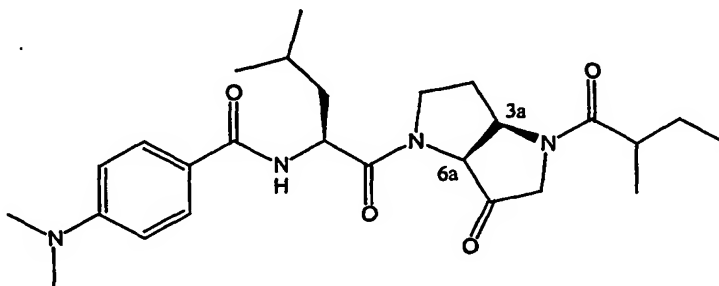
EXAMPLE 228. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-*tert*-butyl-benzamide



-408-

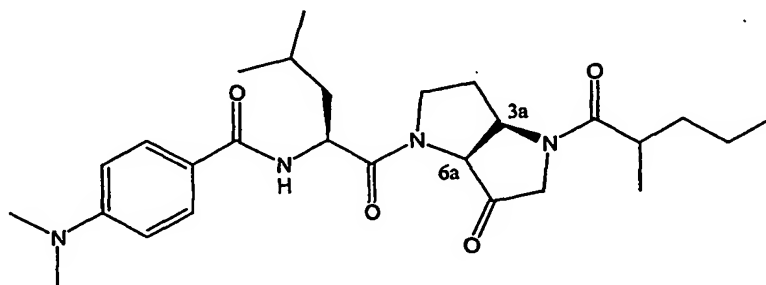
HPLC Rt = 15.47 mins (> 95%), HPLC-MS 513.2 [M + H]⁺.

EXAMPLE 229. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(2-methyl-
5 butyryl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



HPLC Rt = 11.4-11.5 mins (> 80%), HPLC-MS 471.2 [M + H]⁺, 493.2 [M +
10 Na]⁺.

EXAMPLE 230. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[4-(2-methyl-
pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

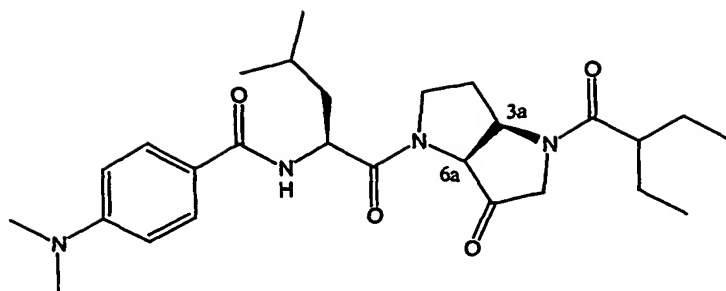


15

HPLC Rt = 12.4-13.3 mins (> 80%), HPLC-MS 485.2 [M + H]⁺.

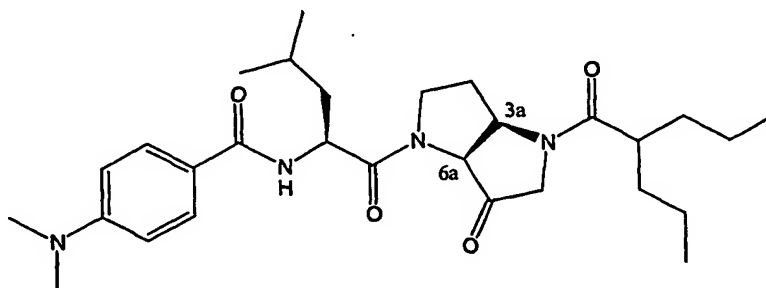
EXAMPLE 231. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-[4-(2-ethyl-butyl)-6-
20 oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

-409-



HPLC Rt = 12.34 mins (> 80%), HPLC-MS 485.2 [M + H]⁺, 991.3 [2M + Na]⁺.

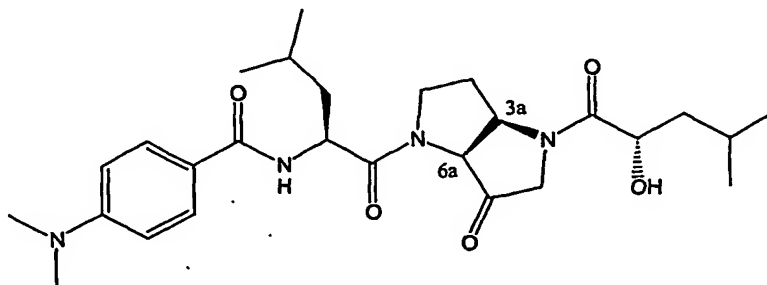
- 5 **EXAMPLE 232.** (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{[(1*S*)-3-methyl-1-[6-oxo-4-(2-propyl-pentanoyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl]-benzamide



10

HPLC Rt = 14.75 mins (> 90%), HPLC-MS 513.2 [M + H]⁺.

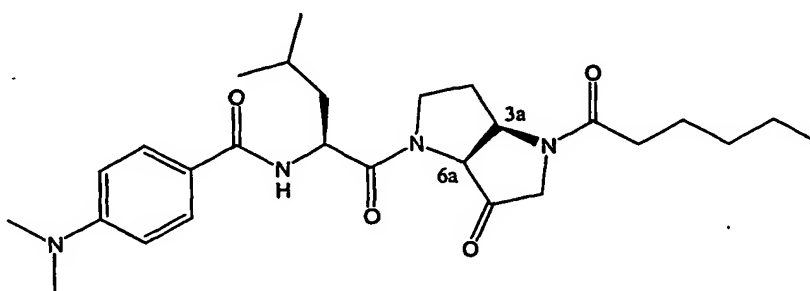
- 15 **EXAMPLE 233.** (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{[(1*S*)-1-[4-((2*S*)-2-hydroxy-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl]-benzamide



-410-

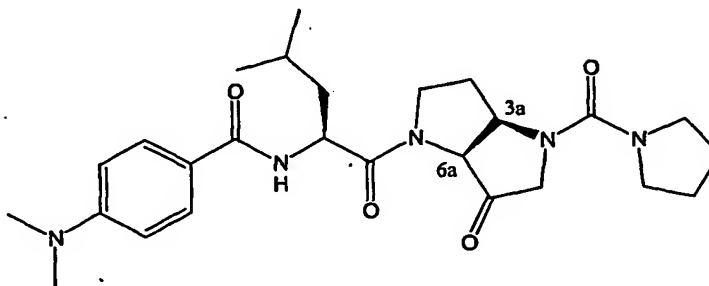
HPLC Rt = 12.04 mins (> 95%), HPLC-MS 501.2 [M + H]⁺, 519.2 [M + H + H₂O]⁺.

5 **EXAMPLE 234.** (3a*R*, 6a*S*)-4-Dimethylamino-*N*-[(1*S*)-1-(4-hexanoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl-butyl]-benzamide



10 HPLC Rt = 13.24 mins (> 95%), HPLC-MS 485.2 [M + H]⁺, 503.2 [M + H + H₂O]⁺.

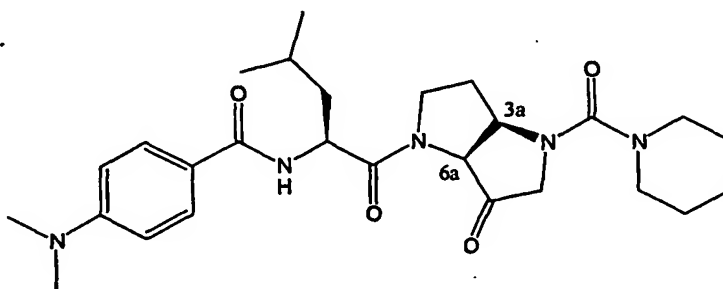
15 **EXAMPLE 235.** (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(pyrrolidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



HPLC Rt = 11.06 mins (> 95%), HPLC-MS 484.1 [M + H]⁺, 989.3 [2M + Na]⁺.

-411-

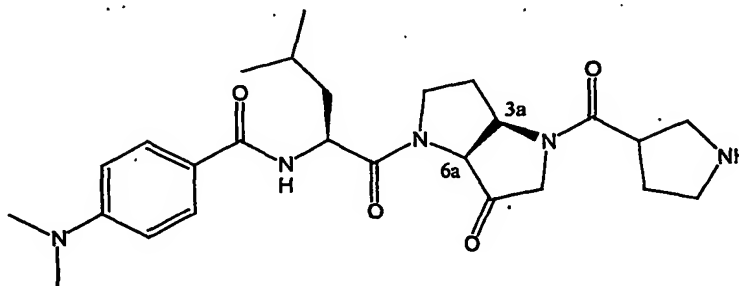
EXAMPLE 236. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(piperidine-1-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



5

HPLC R_t = 12.21 mins (> 95%), HPLC-MS 498.2 $[M + H]^+$, 516.3 $[M + H + H_2O]^+$.

10 EXAMPLE 237. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(pyrrolidine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

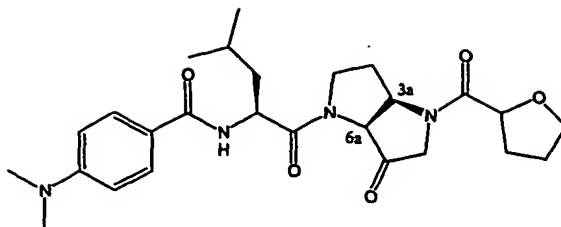


15

HPLC R_t = 8.13 mins (> 95%), HPLC-MS 484.1 $[M + H]^+$, 502.2 $[M + H + H_2O]^+$.

20 EXAMPLE 238. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(tetrahydro-furan-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide

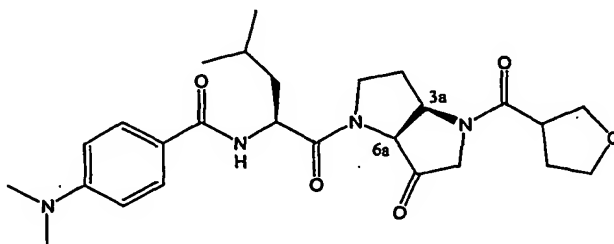
-412-



HPLC Rt = 9.89 mins (> 95%), HPLC-MS 485.1 [M + H]⁺, 503.1 [M + H + H₂O]⁺.

5

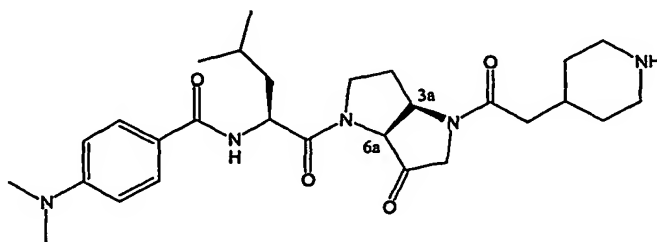
EXAMPLE 239. (3aR, 6aS)-4-Dimethylamino-N-((1S)-3-methyl-1-[6-oxo-4-(tetrahydro-furan-3-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl)-benzamide



10

HPLC Rt = 10.40 mins (> 90%), HPLC-MS 485.1 [M + H]⁺, 503.1 [M + H + H₂O]⁺.

EXAMPLE 240. (3aR, 6aS)-4-Dimethylamino-N-((1S)-3-methyl-1-[6-oxo-4-(2-piperidin-4-yl-acetyl)-hexahydro-pyrrolo[3,2-b]pyrrole-1-carbonyl]-butyl)-benzamide

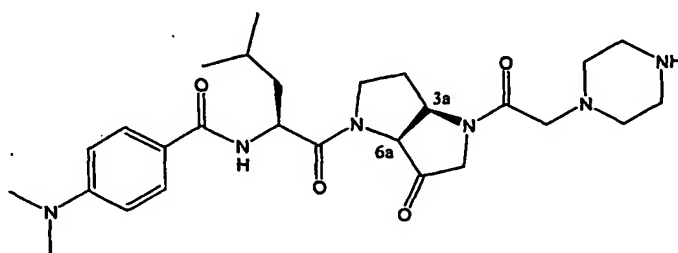


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-413-

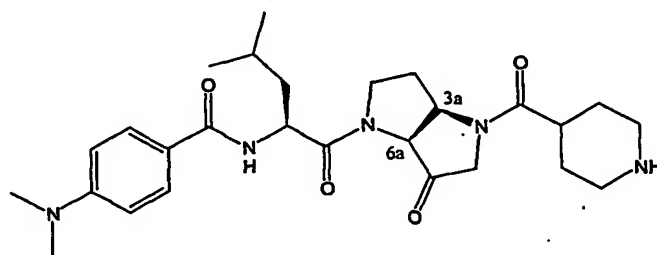
HPLC Rt = 8.8-9.6 mins (> 90%), HPLC-MS 512.2 [M + H]⁺, 530.2 [M + H + H₂O]⁺.

5 EXAMPLE 241. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(2-piperazin-1-yl-acetyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



10 HPLC Rt = 7.3-8.2 mins (> 85%), HPLC-MS 513.1 [M + H]⁺, 531.2 [M + H + H₂O]⁺.

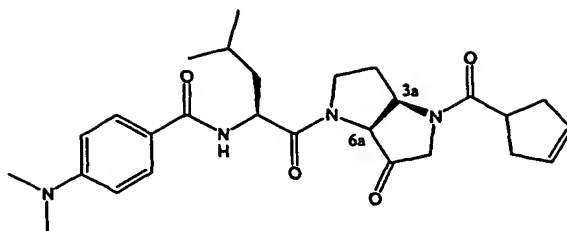
15 EXAMPLE 242. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-3-methyl-1-[6-oxo-4-(piperidine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-butyl}-benzamide



20 HPLC Rt = 8.2-8.9 mins (> 90%), HPLC-MS 498.2 [M + H]⁺, 516.2 [M + H + H₂O]⁺, 995.3 [2M + H]⁺,

EXAMPLE 243. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(Cyclopent-3-enecarbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

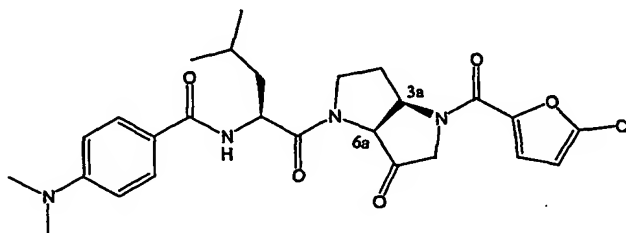
-414-



HPLC Rt = 11.39 mins (> 95%), HPLC-MS 481.2 [M + H]⁺, 983.3 [2M + Na]⁺.

5

EXAMPLE 244. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(5-Chloro-furan-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

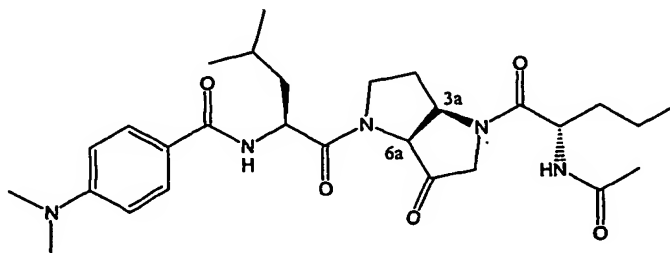


10

HPLC Rt = 13.17 mins (> 90%), HPLC-MS 515.1 [M + H]⁺, 537.1 [M + Na]⁺.

EXAMPLE 245. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-((2*S*)-2-Acetylamino-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-4-dimethylamino-benzamide

15

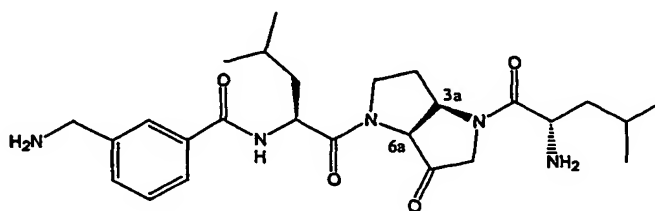


20

HPLC Rt = 11.18 mins (> 90%), HPLC-MS 528.2 [M + H]⁺.

-415-

EXAMPLE 246. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-{(1*S*)-1-[4-((2*S*)-2-amino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-benzamide

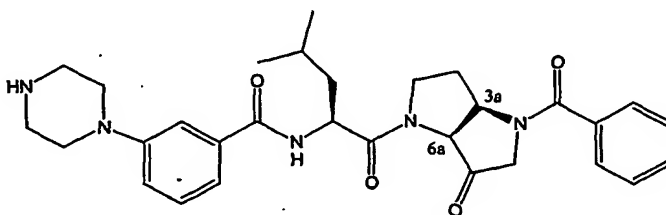


5

HPLC Rt = 8.87 mins (> 95%), HPLC-MS 486.2 [M + H]⁺, 971.4 [2M + H]⁺.

EXAMPLE 247. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrole-1-carbonyl)-3-methyl-butyl]-3-piperazin-1-yl-benzamide

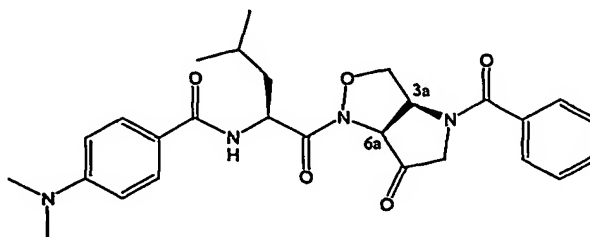
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15

HPLC Rt = 10.92 mins (> 85%), HPLC-MS 532.1 [M + H]⁺, 550.2 [M + H + H₂O]⁺.

EXAMPLE 248. (3a*S*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-2-oxa-1,4-diaza-pentalene-1-carbonyl)-3-methyl-butyl]-4-dimethylamino-benzamide

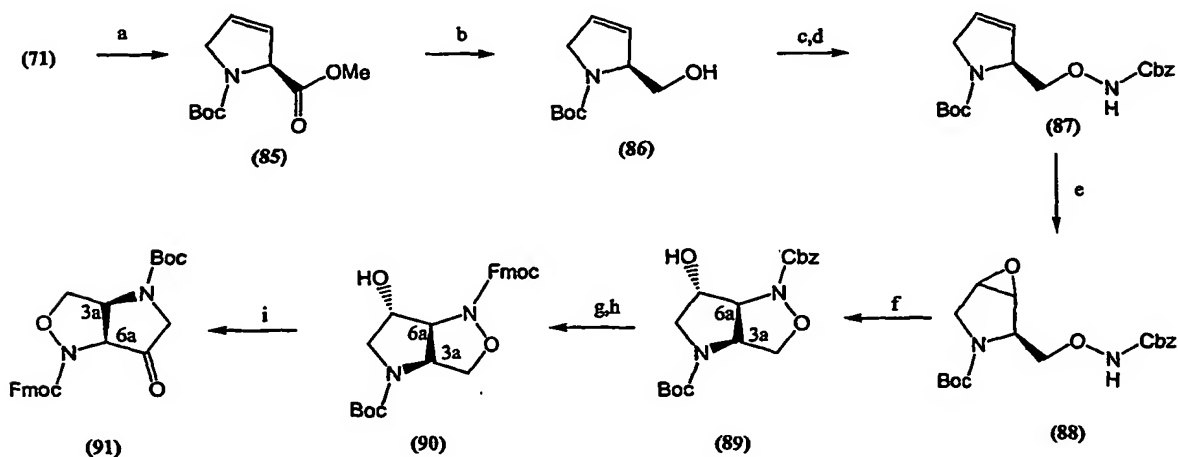


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-416-

HPLC Rt = 13.18 mins (> 95%), HPLC-MS 493.1 [M + H]⁺, 511.1 [M + H + H₂O]⁺.

EXAMPLE 248 was prepared following the general methods detailed for
 5 EXAMPLE 1, but using an alternative building block (3a*S*, 6a*S*)-6-oxo-
 tetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 4-*tert*-butyl ester 1-
 (9H-fluoren-9-ylmethyl) ester (91) prepared following general Scheme 5 and
 Scheme 22. Following solid phase synthesis, the crude product was purified by
 semi-preparative HPLC and lyophilised to give EXAMPLE 248.



10

Scheme 22. (a) Ethereal CH₂N₂, -15 °C to RT. (b) LiBH₄, MeOH, THF or DIBAL-H, THF (c) Methanesulfonyl chloride, triethylamine, DCM (d) Cbz-NH-OH, NaH, 65 °C (e) *m*-Chloroperoxybenzoic acid, DCM. (f) Potassium carbonate, CH₃CN (g) Pd-C, H₂, ethanol. (h) 1.05 eq Fmoc-Cl, 2.1eq Na₂CO₃, 1,4-dioxane, water (i) Dess-Martin periodinane, DCM.

15

Preparation of (S)-2,5-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (85)

20 Ethereal diazomethane [\sim 23 mmol generated from addition of diazald (7.1 g,) in diethyl ether (115 ml) onto sodium hydroxide (8.0 g) in water (14 ml) / ethanol (28 ml) at 65 °C] was added in portions to a stirred solution of (S)-2,5-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester (71) (*ex* Bachem, 4.98 g,

-417-

23.4 mmol) in dichloromethane (100 ml) at 0 °C over 5 minutes. The solution was stirred for 1 hour at 0 °C then glacial acetic acid (0.5 ml) was added dropwise. The product was extracted into dichloromethane (50 ml) then washed with saturated aqueous sodium hydrogen carbonate solution (100 ml), water (100 ml) and brine (100 ml). The organic layer was dried (Na₂SO₄) and the solvents removed *in vacuo* to obtain (S)-2,5-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (85) (4.66 g, 88%), which was used without further purification. TLC (Single spot, R_f = 0.25, EtOAc : heptane 1 : 4), HPLC-MS 172.1 [M + 2H - Bu]⁺, 250.1 [M + Na]⁺, 477.2 [2M + Na]⁺; C₁₁H₁₇NO₄·0.4H₂O req.(*find.*) % C 56.38 (56.47), % H 7.66 (7.25), % N 5.97 (5.88).

Preparation of (S)-2-hydroxymethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (86)

Methanol (1.66 ml, 41 mmol) was added dropwise to a stirred suspension of lithium borohydride (0.90 g, 41 mmol) in tetrahydrofuran (20 ml) over 2 minutes under an atmosphere of argon, followed by a solution of (S)-2,5-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (85) (4.65 g, 20.5 mmol) in tetrahydrofuran (50 ml) over 15 minutes. The mixture was stirred for 70 minutes then poured into water (125 ml). The product was extracted into dichloromethane (3x 100 ml), dried (Na₂SO₄), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 15 : 85 to 25 : 75 to give (S)-2-hydroxymethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (86) as a colourless oil (3.75 g, 92%), [α]_D²² -136° (c=1, CHCl₃). TLC (Single spot, R_f = 0.30, EtOAc : heptane 2 : 3), HPLC-MS 222.1 [M + Na]⁺, 421.1 [2M + Na]⁺; C₁₀H₁₇NO₃·0.3H₂O req.(*find.*) % C 58.72 (58.82), % H 8.67 (8.35), % N 6.85 (6.88); d_H (500 MHz, CDCl₃) mixture of rotamers (major : minor = 4 : 1) 1.47 and 1.49 (9H total, each s, (CH₃)₃C), 3.55 (0.8H, ddd, J = 11.1, 7.7, 1.1 Hz, CH₂OH major), 3.61-3.66 (0.2H, m, CH₂OH minor), 3.77 (1H, m, CH₂OH), 3.95-4.09 (1H, m, H-5), 4.14-4.19 (0.8H, m, H-5 major), 4.24-4.30 (0.2H, m, H-5 minor), 4.58 (0.2H, br. s, H-2 minor), 4.64 (1H,

-418-

m, OH), 4.69-4.75 (0.8H, m, H-2 major), 5.57-5.63 and 5.78-5.82 (each 0.8H, m, H-3 and H-4 major), 5.65-5.70 and 5.89-5.94 (each 0.2H, m, H-3 and H-4 minor).

Alternative preparation of (S)-hydroxymethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (86)

A solution of diisobutylaluminium hydride (1.0M in tetrahydrofuran, 18.7 ml, 18.7 mmol) was added dropwise to a stirred solution of (S)-2,5-dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (85) (*ex* Bachem, 1.06 g, 4.67 mmol) in tetrahydrofuran (15 ml) at -70 °C over 45 minutes under an atmosphere of argon. The mixture was stirred for 15 minutes at -70 °C then at ambient temperature for 3.25 hours before cooling to 0 °C and adding ethyl acetate (10 ml) dropwise followed by saturated aqueous sodium potassium tartrate solution (60 ml), ethyl acetate (65 ml) and brine (60 ml). The organic layer was separated then the aqueous layer extracted with ethyl acetate (60 ml). The organic layers were combined then washed with brine (50 ml), dried (MgSO₄), and solvents removed *in vacuo* to leave a residue which was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 15 : 85 to 25 : 75 to give (S)-hydroxymethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (86) as a colourless oil (0.34 g, 36%), $[\alpha]_D^{22} -120.5^\circ$ ($c=1$, CHCl₃). TLC (Single spot, $R_f = 0.30$, EtOAc : heptane 2 : 3), analytical HPLC $R_t = 9.375$ min; HPLC-MS 222.1 $[M + Na]^+$, 421.2 $[2M + Na]^+$.

Preparation of (S)-(N'-benzyloxycarbonylaminooxymethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (87)

i) Pyridine (7.6 ml, 94.2 mmol) was added to a solution of (S)-hydroxymethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (86) (3.75 g, 18.8 mmol) in dichloromethane whilst stirring at 0 °C followed by methanesulfonyl chloride (1.53 ml, 19.8 mmol) in portions over 10 minutes. The mixture was stirred for 1 hour at 0 °C then at ambient temperature for 14 hours. The product was extracted into dichloromethane (250 ml), washed with ice-chilled hydrochloric acid (1M, 2x

-419-

- 125 ml) and aqueous saturated sodium hydrogen carbonate solution (125 ml), dried (Na_2SO_4), and solvents removed *in vacuo* to leave (*S*)-methanesulfonyloxymethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester as an oily residue (5.2 g, 100%) which was used without further purification. TLC (Single spot, $R_f = 0.20$, EtOAc : heptane 3 : 7), analytical HPLC $R_t = 12.785$ min; HPLC-MS 222.0 $[\text{M} + 2\text{H} - \text{Bu}]^+$, 577.1 $[2\text{M} + \text{Na}]^+$; d_H (500 MHz, CDCl_3) mixture of rotamers (major : minor = 4 : 3) 1.45 and 1.49 (9H total, each s, $(\text{CH}_3)_3\text{C}$), 2.96 (3H, s, SO_2CH_3), 4.02-4.03 (0.43H, m, H-5 minor), 4.04-4.07 (0.57H, m, H-5 major), 4.12-4.57 (3H, m, H-5, CH_2OS), 4.67 (0.43H, br. s, H-2), 4.74 (0.57H, br. s, H-2), 5.73-5.98 (2H, m, H-3 and H-4); d_C (125 MHz, CDCl_3) 28.41 ($\text{C}(\text{CH}_3)_3$), 36.99, 37.46 (SCH_3), 53.80, 53.95 (C-5), 62.90, 63.02 (C-2), 69.14, 69.34 (CH_2OS), 80.12, 80.62 ($\text{C}(\text{CH}_3)_3$), 126.08, 126.16 and 128.27, 128.36 (C-3 and C-4), 153.73, 154.13 (q, $\text{NC}=\text{O}$).
- ii) Sodium hydride (60% dispersion in oil, 3.0 g, 75.1 mmol) was added to a stirred solution of benzyl *N*-hydroxycarbamate (13.2 g, 78.8 mmol) in tetrahydrofuran (200 ml) at 0 °C in portions over 30 minutes under an atmosphere of argon. The mixture was stirred for 5 minutes at 0 °C then a solution of (*S*)-methanesulfonyloxymethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (5.2 g, 18.6 mmol, prepared as above) in tetrahydrofuran (175 ml) was added dropwise over 15 minutes. The resulting cloudy suspension was stirred for 1 hour at ambient temperature then at 65 °C for 4 hours, followed by 14 hours at ambient temperature then 7 hours at 65 °C. The product was extracted into dichloromethane (250 ml) then cautiously washed with water (250 ml). The aqueous layer was extracted with dichloromethane (250 ml) then the combined organic layers washed with water (3x 150 ml) and brine (250 ml), dried (Na_2SO_4), and the solvents removed *in vacuo*. The residue was purified twice by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 25 : 75 to 30 : 70 then 0 : 100 to 25 : 75 to give (*S*)-(N'-benzyloxy carbonylaminooxymethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (87) as a colourless oil (1.67 g, 26%) together with recovered (*S*)-methanesulfonyloxymethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester

-420-

(2.44 g, 47%). Data for (S)-(N'-benzyloxycarbonylaminooxymethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (87). TLC (Single spot, R_f = 0.35, EtOAc : heptane 2 : 3), analytical HPLC R_t = 17.141 min; HPLC-MS 349.1 [M + H]⁺, 371.1 [M + Na]⁺, 719.2 [2M + Na]⁺; Elemental analysis C₁₈H₂₄N₂O₅ req.(*fund.*) % C 62.05 (62.18), % H 6.94 (7.05), % N 8.04 (7.90); HRMS C₁₈H₂₄N₂O₅Na req. 371.1583, *fund.* 371.1590 (1.83ppm); d_H (500 MHz, CDCl₃) mixture of rotamers (major : minor = 2 : 1) 1.46 (9H, s, (CH₃)₃C), 3.67 (0.67H, dd, J = 11.45 and 7.6 Hz, CH₂ONH major), 3.89 (0.33H, dd, J = 10.2 and 6.2 Hz, CH₂ONH minor), 3.99 (0.67H, dd, J = 11.45 and 3.7 Hz, CH₂ONH major), 3.95-4.10 (1H, m, H-5), 4.08-4.13 (0.33H, m, CH₂ONH minor), 4.21 (0.67H, dd, J = 15.7 and 1.8 Hz, H-5 major), 4.20-4.26 (0.33H, m, H-5, minor), 4.63 (0.33H, br. s, H-2 minor), 4.85-4.90 (0.67H, m, H-2 m, major), 5.13-5.18 (2H, m, OCH₂Ph), 5.68-5.73 and 5.82-5.87 (2H, m, H-3 and H-4), 7.30-7.37 (5H, aromatics), 7.52 (0.33H, br. s, NH, minor), 8.69 (0.67H, br. s, NH, major); d_C (125 MHz, CDCl₃) 28.40 (C(CH₃)₃), 53.57, 53.78 (C-5), 62.18, 62.76 (C-2), 67.13, 67.55 (OCH₂Ph), 77.27, 77.86 (CH₂ONH), 80.07 (C(CH₃)₃), 126.62, 126.72, 127.47, 127.85, 128.12, 128.24, 128.50, 128.54, 128.58 (C-3, C-4, aromatic CH), 135.48, 135.87, 136.18 (aromatic quaternary), 154.04, 155.24 (CH₂NC=O), 156.94, 157.39 (ONC=O).

20

Preparation of (2R)-(N'-benzyloxycarbonylaminooxymethyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (88)

meta-Chloroperoxybenzoic acid (57-86%, 1.9g, ~7.7 mmol) was added in portions under an atmosphere of argon over 15 minutes to a stirred solution of (S)-(N'-benzyloxycarbonylaminooxymethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (87) (600 mg, 1.72 mmol) in dichloromethane (12 ml). The mixture was stirred for 14 hours then the product was extracted into dichloromethane (50 ml), washed with aqueous saturated sodium hydrogen carbonate solution (2x 30 ml), dried (Na₂SO₄), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane 0 : 100 to 30 : 70 to give (2R)-(N'-benzyloxycarbonylaminooxymethyl)-6-oxa-3-

-421-

azabicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (88) as a colourless oil (390 mg, 62%). TLC (Single spot, R_f = 0.35, EtOAc : heptane 2 : 3), analytical HPLC R_t = 15.733 min; HPLC-MS 265.1 $[M + 2H - Boc]^+$, 309.0 $[M + 2H - Bu]^+$, 387.1 $[M + Na]^+$, 751.2 $[2M + Na]^+$; $C_{18}H_{24}N_2O_6 \cdot 0.4H_2O$ req.(*find.*) % C 58.21 (58.24), % H 6.73 (6.62), % N 7.54 (7.57); HRMS $C_{18}H_{24}N_2O_6Na$ req. 387.1532, *find.* 387.1534 (0.42ppm).

Preparation of (3a*S*, 6*S*, 6a*S*)-6-hydroxytetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester (89)

10

Potassium carbonate (1.06 g, 7.7 mmol) was added to a stirred solution of (2*R*)-(N'-benzyloxycarbonylaminooxymethyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (88) (280 mg, 0.77 mmol) in acetonitrile (4 ml) under an atmosphere of argon. The suspension was stirred for 5 hours then the product was extracted into dichloromethane (30 ml) and washed with water (10 ml). The aqueous layer was extracted with dichloromethane (10 ml) then the combined organic layers washed with water (10 ml), dried (Na_2SO_4), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 30 : 70 to give (3a*S*, 6*S*, 6a*S*)-6-hydroxytetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester (89) as a colourless oil (141 mg, 50%) together with recovered (1*S*, 2*R*, 5*R*)-2-(N'-benzyloxycarbonylaminooxymethyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (88) as a colourless oil (71 mg, 25%). Data for (3a*S*, 6*S*, 6a*S*)-6-hydroxytetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester (89). TLC (Single spot, R_f = 0.20, EtOAc : heptane 2 : 3), analytical HPLC R_t = 14.994 min; HPLC-MS 265.1 $[M + 2H - Boc]^+$, 309.1 $[M + 2H - Bu]^+$, 751.2 $[2M + Na]^+$; HRMS $C_{18}H_{24}N_2O_6Na$ req. 387.1532, *find.* 387.1529 (-0.87ppm); d_H (500 MHz, $CDCl_3$) mixture of rotamers, *tentative proton assignment*, 1.45 (9H, s, $C(CH_3)_3$), 2.28 (1H, d, J = 3.9 Hz, OH), 3.45-4.81 (7H, m, BocNCHCH₂, BocNCH, BocNCH₂, CHOH, CbzNCH), 5.12-5.26 (2H, m, OCH₂Ph), 7.32-7.42 (5H, aromatics). Data for (1*S*, 2*R*, 5*R*)-2-(N'-benzyloxycarbonylaminooxymethyl)-

-422-

6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (88). TLC (Single spot, $R_f = 0.35$, EtOAc : heptane 40 : 60), HPLC-MS 265.1 $[M + 2H - \text{Boc}]^+$, 309.1 $[M + 2H - \text{Bu}]^+$, 387.1 $[M + \text{Na}]^+$, 751.2 $[2M + \text{Na}]^+$; d_H (500 MHz, CDCl_3) mixture of rotamers, *tentative proton assignment*, 1.41 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.39-3.72 (3H, m, H-2 and H-5), 3.90-4.41 (4H, m, H-3, H-4 and CH_2ON), 5.12-5.20 (2H, m, OCH_2Ph), 7.31-7.39 (5H, aromatics), 7.60 and 8.0 (0.8H total, each br. s, NH).

Preparation of (3aS, 6S, 6aS)-6-hydroxytetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 4-*tert*-butyl ester 1-(9H-fluoren-9-ylmethyl) ester (90)

Ethanol (2.5 ml) was cautiously added to a stirred mixture of (3aS, 6S, 6aS)-6-hydroxytetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester (89) (43 mg, 0.118 mmol) and 10% palladium on charcoal (5 mg) under an atmosphere of argon at 0 °C. The argon was replaced by hydrogen then the suspension was stirred at ambient temperature for 45 minutes then the hydrogen was replaced by argon before filtering the mixture through celite *in vacuo*. The filter cake was washed with ethanol (25 ml) then solvents removed *in vacuo* from the filtrate to leave (3aS, 6S, 6aS)-6-hydroxyhexahydro-2-oxa-1,4-diazapentalene-4-carboxylic acid *tert*-butyl ester as an oily residue (28 mg), which was used without further purification. HPLC-MS 175.1 $[M + 2H - \text{Bu}]^+$, 483.2 $[2M + \text{Na}]^+$. A solution of sodium carbonate (31 mg, 0.295 mmol) in water (1.75 ml) was added whilst stirring to a solution of (3aS, 6S, 6aS)-6-hydroxyhexahydro-2-oxa-1,4-diazapentalene-4-carboxylic acid *tert*-butyl ester (28 mg) in 1,4-dioxane (1.0 ml). The mixture was cooled to 0 °C then a solution of Fmoc-Cl (34 mg, 0.132 mmol) in 1,4-dioxane (0.75 ml) was added dropwise over 40 minutes. The mixture was stirred at 0 °C for 2.25 hours then at ambient temperature for 30 minutes. Water (20 ml) was added then the product extracted into dichloromethane (3x 15 ml), dried (Na_2SO_4), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 30 : 70 to give (3aS, 6S, 6aS)-6-hydroxytetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 4-*tert*-butyl

-423-

ester 1-(9H-fluoren-9-ylmethyl) ester (90) as a white solid (40 mg, 75%). TLC (Single spot, $R_f = 0.20$, EtOAc : heptane 3 : 7), analytical HPLC $R_t = 18.217$ min; HPLC-MS 475.1 $[M + Na]^+$, 927.2 $[2M + Na]^+$; $C_{25}H_{28}N_2O_6 \cdot 0.5EtOAc$ req.(*find.*) % C 65.35 (64.85), % H 6.50 (6.21), % N 5.64 (5.66).

5

Preparation of (3a*S*, 6a*S*)-6-oxo-tetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 4-*tert*-butyl ester 1-(9H-fluoren-9-ylmethyl) ester (91)

Dess-Martin periodinane (73 mg, 0.170 mmol) was added to a stirred solution of (3a*S*, 6*S*, 6a*S*)-6-hydroxytetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 4-*tert*-butyl ester 1-(9H-fluoren-9-ylmethyl) ester (90) (39 mg, 0.086 mmol) in dichloromethane (1.25 ml). The mixture was stirred for 2.5 hours, stored at -80°C for 14 hours, and then purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 5 : 95 to 15 : 85 to give (3a*S*, 6a*S*)-6-oxo-tetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 4-*tert*-butyl ester 1-(9H-fluoren-9-ylmethyl) ester (91) as a white solid (31 mg, 80%). TLC (Single spot, $R_f = 0.30$, EtOAc : heptane 2 : 3), analytical HPLC broad peak $R_t = 19.57$ -22.15 min; HPLC-MS single broad main UV peak, 473.1 $[M + Na]^+$, 491.1 $[M + H_2O + Na]^+$, 923.1 $[2M + Na]^+$, 959.1 $[2M + 2H_2O + Na]^+$; HRMS $C_{25}H_{26}N_2O_6Na$ req. 473.1689, *find.* 473.1690 (0.24ppm); d_H (500 MHz, $CDCl_3$) mixture of rotamers major : minor 1.5 : 1, 1.48 (5.4H, s, $C(CH_3)_3$ major), 1.50 (3.6H, s, $C(CH_3)_3$ minor), 3.49-3.58 (1H, m, $BocNCHCH_2$), 3.78-3.92 (2H, m, $BocNCH_2$), 4.13 (0.4H, d, $J = 9.5\text{Hz}$, $BocNCHCH_2$ [minor]), 4.20-4.29 (1.6H, m, $Fmoc-CH$ and $BocNCHCH_2$ [major]), 4.46-4.52 (1H, m, $Fmoc-CH_2$), 4.60-4.74 (2.4H, m, $Fmoc-CH_2$, $FmocNCH$, $BocNCH$ [minor]), 4.83 (0.6H, dd, $J = 7.5$ and 4.3Hz , $BocNCH$ [major]), 7.29-7.78 (8H, aromatic); d_C (125 MHz, $CDCl_3$) 28.38, 28.31 ($C(CH_3)_3$), 46.96, 47.05 ($Fmoc-\underline{CH}$), 52.40, 52.93 ($BocN\underline{CH}_2$), 61.95 ($BocN\underline{CH}$), 64.48, 65.31 ($FmocN\underline{CH}$), 68.59, 68.76 ($Fmoc-\underline{CH}_2$), 77.17, 77.31 ($BocNCH\underline{CH}_2$), 81.61 ($\underline{C(CH_3)_3}$), 120.02, 125.11, 125.35, 127.21, 127.28, 127.98 ($Fmoc$ aromatic \underline{CH}), 141.29, 141.33, 143.04, 143.12 ($Fmoc$ quaternary), 153.09, 154.00 ($Boc \underline{C=O}$), 157.64 ($Fmoc \underline{C=O}$), 204.85, 205.44 ($\underline{C=O}$).

-424-

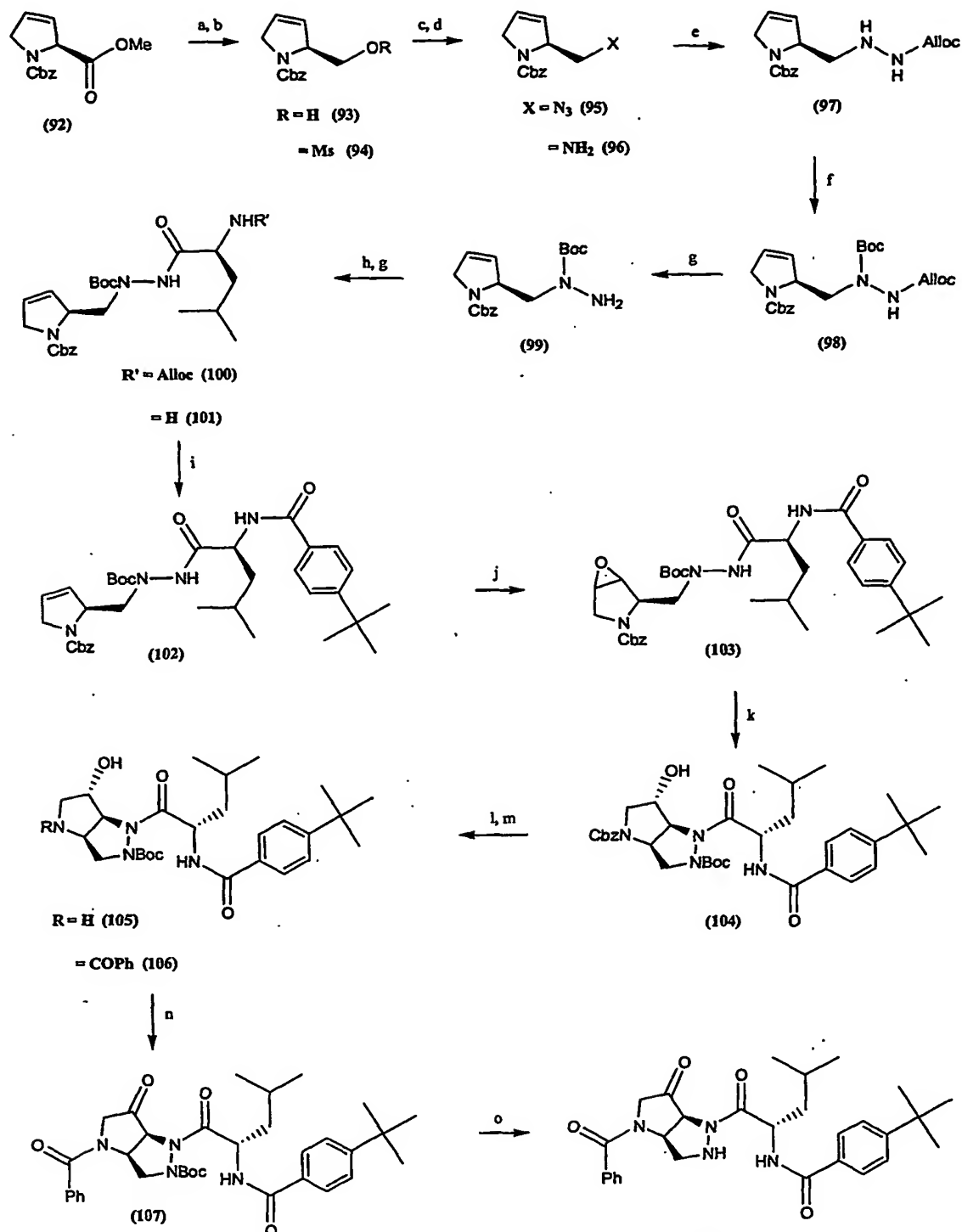
Broadly following the general details from Scheme 6, the required bicycle building block (3aS, 6aS)-6-oxo-tetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 4-*tert*-butyl ester 1-(9H-fluoren-9-ylmethyl) ester (91) was converted to the corresponding equivalent of building block-linker construct (27) (where Pg₂ is *tert*-butoxycarbonyl) as follows:

A solution of sodium acetate trihydrate (24 mg, 0.173 mmol) in water (0.25 ml) was added to a solution of (3aS, 6aS)-6-oxo-tetrahydro-2-oxa-1,4-diazapentalene-1,4-dicarboxylic acid 4-*tert*-butyl ester 1-(9H-fluoren-9-ylmethyl) ester (91) (26 mg, 0.058mmol) and 4-[[[(hydrazinocarbonyl)amino]methyl]cyclohexane carboxylic acid. trifluoroacetate (Murphy, A. M., *et al*, J. Am. Chem. Soc, 114, 3156-3157, 1992) (38 mg, 0.116 mmol) in ethanol (1.75 ml). The reaction heated at 75 °C in a sealed tube for 1.5 hour. The product was extracted into chloroform (50 ml) then washed with hydrochloric acid (0.1M, 2 x 25 ml), saturated aqueous sodium chloride solution (30 ml) then dried (Na₂SO₄) and the solvent removed *in vacuo* to leave the product as a white solid (37 mg, ~100%). Analytical HPLC has main UV peaks with Rt = 20.223 and 21.596mins and HPLC-MS (main UV peaks each with 648.2 [M+H]⁺).

Following the general details from Scheme 6, the corresponding building block-linker construct was attached to the solid phase providing loaded building block-linker construct following standard loading protocols and indicated quantitative loading.

EXAMPLES 249a to 249c were prepared entirely by solution phase synthesis methods (broadly defined by the general strategy detailed in Scheme 4) following Schemes 23 to 25 and have utility as inhibitors of cathepsin K with Ki < 1000nM.

-425-



EXAMPLE 249a

Scheme 23. (a) DIBAL-H, THF or LiBH₄, MeOH, THF (b) Methanesulfonyl chloride, triethylamine, DCM (c) Sodium azide, DMF, 110°C (d) Ph₃P / H₂O, 1,4-dioxane, 50°C (e) 3-Phenylloxaziridine-2-carboxylic acid allyl ester, DCM (f) (Boc)₂O, DCM, 60°C (g) Pd(PPh₃)₄,

-426-

PhSiH₃, DCM (h) Alloc-Leu-F, DMF (i) 4-*tert*-Butylbenzoic acid, HBTU, HOBT, NMM, DMF (j) *m*-Chloroperoxybenzoic acid, DCM. (k) Potassium carbonate, CH₃CN, 60°C (l) Pd-C, H₂, ethanol (m) (PhCO)₂O, DMF (n) Dess-Martin periodinane, DCM (o) TFA, DCM

5 Preparation of (*S*)-2,5-dihydropyrrole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (92)

Carbonic acid benzyl ester 2,5-dioxopyrrolidin-1-yl ester (8.45 g, 33.9 mmol) then triethylamine (10.8 ml, 77 mmol) were added dropwise to a stirred solution of (*S*)-2,5-dihydropyrrole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester hydrochloride (5.0 g, 30.6 mmol) and THF : water (1 : 1, 306 ml) at 0 °C. The mixture was stirred at ambient temperature for 12 hours then half of the solvent was removed *in vacuo*. The product was extracted into *tert*-butyl methyl ether (3 x 100 ml) then the combined organic layers were washed with 5% hydrochloric acid (100 ml), 5% aqueous sodium hydrogen carbonate solution (100 ml) and brine (100 ml), dried (MgSO₄), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with heptane : *tert*-butyl methyl ether 2 : 1 to give (*S*)-2,5-dihydro pyrrole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (92) as a pale yellow oil (7.9 g, 99%). TLC (*R_f* = 0.30, heptane : *tert*-butyl methyl ether 1 : 1), analytical HPLC single peak with *R_t* = 13.935 min, HPLC-MS 262.0 [M + H]⁺, 284.0 [M + Na]⁺, 545.1 [2M + Na]⁺. δ_H (500 MHz, CDCl₃) approximately 1 : 1 mixture of rotamers, 3.57 and 3.64 (3H, each s, OCH₃), 4.22-4.36 (2H, m, H-5), 5.03-5.14 (3H, m, OCH₂Ph and H-2), 5.69-5.78 and 5.92-5.99 (2H, each m, H-3 and H-4), 7.29-7.39 (5H, aromatics); δ_C (125 MHz, CDCl₃) 52.25 and 52.42 (OCH₃), 53.36 and 53.85 (C-5), 66.25 and 66.56 (C-2), 67.09 and 67.16 (PhCH₂O), 124.66, 127.80, 127.91, 127.98, 128.03, 128.40, 128.46, 129.09 and 129.18 (C-3, C-4 and aromatic CH), 136.43 and 136.51 (aromatic quaternary), 153.91 and 154.36 (NC=O), 170.38 and 170.62 (CHC=O).

30

Preparation of (*S*)-2-hydroxymethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (93)

-427-

Diisobutylaluminium hydride (1.5M in toluene, 2.62 ml, 3.93 mmol) was added dropwise over 20 minutes to a stirred solution of (*S*)-2,5-dihydropyrrole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (**92**) (0.41 g, 1.57 mmol) in THF (15 ml), at -78°C under an atmosphere of argon. The mixture was stirred for 2 hours at -78°C then at ambient temperature for 18 hours. Saturated aqueous potassium sodium tartrate solution (40 ml) was added slowly to the mixture, followed by ethyl acetate (40ml) and magnesium sulphate ~5 g. The resultant slurry was vigorously stirred for 2 hours, then filtered and the filter cake washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane 1 : 4 to give (*S*)-2-hydroxymethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (**93**) as a pale yellow oil (130 mg, 36%). TLC (R_f = 0.30, heptane : ethyl acetate 1 : 1), analytical HPLC single peak with R_t = 11.033 min, HPLC-MS 234.1 [$\text{M} + \text{H}$]⁺, 256.0 [$\text{M} + \text{Na}$]⁺, 489.1 [$2\text{M} + \text{Na}$]⁺. d_H (500 MHz, CDCl_3) approximately 4 : 1 mixture of rotamers, 3.58-3.66 (1H, m, CH_2OH), 3.77-3.85 (1H, m, CH_2OH), 4.14-4.32 (3H, m, CH_2OH and H-5), 4.63-4.68 (0.2H, br. s, H-2 minor), 4.76-4.81 (0.8H, m, H-2 major), 5.14-5.21 (2H, m, OCH_2Ph), 5.63-5.66 and 5.81-5.85 (1.6H, m, H-3 and H-4 major), 5.69-5.73 and 5.90-5.96 (0.4H, m, H-3 and H-4 minor), 7.29-7.39 (5H, aromatics); d_C (125 MHz, CDCl_3) 53.98 (major) and 54.59 (minor) (C-5), 64.27 (minor) and 66.65 (major) (CH_2OH), 66.11 (minor) and 68.08 (major) (C-2), 67.41 (PhCH_2O), 126.67, 126.70, 126.96, 127.19, 127.40, 127.62, 127.95, 128.17, 128.54 and 128.60 (C-3, C-4 and aromatic CH), 136.30 (aromatic quaternary), 156.68 (NC=O).

Alternative preparation of (*S*)-2-hydroxymethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (**93**)

Methanol (2.43 ml) followed by a solution of (*S*)-2,5-dihydropyrrole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (**92**) (7.90 g, 30.2 mmol) in THF (125 ml) were added dropwise to a stirred suspension of lithium borohydride (1.32 g, 60.5 mmol) in THF (45 ml). The mixture was stirred for 1 hour then

-428-

water (10 ml) cautiously added dropwise. The product was extracted into *tert*-butyl methyl ether (3 x 100 ml) then the combined organic layers dried (MgSO₄), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with heptane : ethyl acetate 4 : 1 to give (S)-2-hydroxymethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (93) as a pale yellow oil (6.38 g, 90%). TLC (R_f = 0.30, heptane : ethyl acetate 1 : 1), analytical HPLC single peak with R_t = 11.036 min, HPLC-MS 234.1 [M + H]⁺, 256.0 [M + Na]⁺, 489.1 [2M + Na]⁺.

10 **Preparation of (S)-2-methanesulfonyloxymethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (94)**

Triethylamine (337 μ l, 2.4 mmol) was added dropwise to a stirred solution of (S)-2-hydroxymethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (93) (0.35 g, 1.50 mmol) and methanesulfonyl chloride (174 μ l, 2.25 mmol) in dichloromethane (10 ml) at 0 °C. The mixture was stirred for 30 minutes then washed with water (10 ml) and brine (10 ml), dried (Na₂SO₄), and the solvents removed *in vacuo* to give (S)-2-methanesulfonyloxymethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (94) as a pale yellow oil (443 mg, 95%) which was used without further purification. TLC (R_f = 0.30, heptane : ethyl acetate 1 : 1), analytical HPLC single peak with R_t = 14.115 min, HPLC-MS 312.0 [M + H]⁺, 334.0 [M + Na]⁺, 645.1 [2M + Na]⁺.

25 **Preparation of (S)-2-azidomethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (95)**

Sodium azide (8.89 g, 137 mmol) was added to a stirred solution of (S)-2-methanesulfonyloxymethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (94) (8.52 g, 27.4 mmol) in DMF (150 ml). The reaction mixture was stirred at 110 °C for 1 hour. The solvent was removed *in vacuo* then the product extracted into ethyl acetate (300 ml), washed with water (300 ml), brine (200 ml), dried (MgSO₄), and the solvents removed *in vacuo*. The residue was purified by flash

-429-

chromatography over silica eluting with heptane : ethyl acetate 9 : 1 to give (*S*)-2-azidomethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (**95**) as a pale yellow oil (5.05 g, 72 %). TLC (R_f = 0.65, heptane : ethyl acetate 1 : 1), analytical HPLC single peak with R_t = 17.855 min, HPLC-MS 259.0 $[M + H]^+$, 281.0 $[M + Na]^+$, 539.1 $[2M + Na]^+$.

Preparation of (*S*)-2-aminomethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (96**)**

Triphenylphosphine (3.20 g, 12.2 mmol) was added to a stirred solution of (*S*)-2-azidomethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (**95**) (2.10 g, 8.13 mmol) in THF (170 ml) containing water (2 ml). The mixture was stirred at 50 °C for 2.5 hours then at ambient temperature 16 hours. The solvents were removed *in vacuo* then the residue was purified by flash chromatography over silica eluting with dichloromethane : methanol 99 : 1 to 95 : 5 mixtures to give (*S*)-2-aminomethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (**96**) as a pale yellow oil (2.15 g) which was contaminated with triphenylphosphine oxide. The pale yellow oil was dissolved in *tert*-butyl methyl ether (15 ml) then cooled to 0 °C before adding HCl in 1,4-dioxane (4M, 5 ml) followed by iced-water (20ml). The aqueous layer was extracted with *tert*-butyl methyl ether (3 x 20 ml), then the pH adjusted to ~12 using 1M aqueous sodium hydroxide solution. The product was then extracted into dichloromethane (3 x 50 ml) and the combined dichloromethane layers were dried (MgSO₄), and the solvents removed *in vacuo* to give (*S*)-2-aminomethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (**96**) as a pale yellow oil (1.40 g, 74%). TLC (R_f = 0.20, methanol : dichloromethane 1 : 9), HPLC-MS 233.1 $[M + H]^+$, 255.1 $[M + Na]^+$, 487.1 $[2M + Na]^+$. d_H (500 MHz, D₆-DMSO) 1.30-2.10 (1H, br. s, CH₂NH₂), 3.00-3.70 (1H, br. s, CH₂NH₂), 2.64-2.75 (1H, m, CH₂NH₂), 2.79-2.88 (1H, m, CH₂NH₂), 4.00-4.21 (2H, m, H-5), 4.42-4.47 (1H, m, H-2), 5.05-5.16 (2H, m, PhCH₂O), 5.84-6.01 (2H, m, H-4 and H-5), 7.31-7.40 (5H, aromatics); d_C (125 MHz, D₆-DMSO) 43.91 and 44.85 (CH₂NH₂), 53.86 and 54.47 (C-5), 65.81 and 65.99 (PhCH₂O), 66.41 and 67.17 (C-2), 126.30, 126.36, 127.55, 127.58, 127.84, 127.86, 128.48, 128.51, 128.83

-430-

and 129.06 (C-3, C-4 and aromatic $\underline{\text{CH}}$), 137.13 and 137.17 (aromatic quaternary), 153.82 and 153.97 (NC=O).

5 **Preparation of (S)-2-(N'-allyloxycarbonylhydrazinomethyl)-2,5-dihydro
pyrrole-1-carboxylic acid benzyl ester (97)**

i) Preparation of 3-phenyloxaziridine-2-carboxylic acid allyl ester

10 Ice-chilled sodium hydroxide (2M, 50 ml, 100 mmol) was added to a vigorously stirred solution of benzaldehyde (5.3 g, 50 mmol) in diethyl ether (50 ml) at ambient temperature, then ice-chilled solutions of hydroxylamine-O-sulfuric acid (6.0 g, 53 mmol) in water (50 ml) and sodium hydroxide (2M, 25 ml, 50 mmol) were added simultaneously over 20 minutes. Allyl chloroformate (5.31 ml, 50 mmol) was added dropwise over 5 minutes then the mixture was stirred at 0 °C
15 for 10 minutes before separating the ethereal layer. The aqueous phase was extracted with diethyl ether (2 x 25 ml), then the combined organic layers stirred at 0 °C for 10 minutes with a solution of hydroxylamine-O-sulfuric acid (2.5 g, 21 mmol) in water (25 ml). The phases were separated, then the aqueous phase extracted with diethyl ether (2 x 25 ml). The combined ethereal layers were dried
20 (MgSO_4), and the solvents removed *in vacuo*. The brown oily residue was purified by flash chromatography over silica eluting with heptane : ethyl acetate 9 : 1 to give 3-phenyloxaziridine-2-carboxylic acid allyl ester as a pale yellow oil (1.44 g, 14%). TLC (R_f = 0.7, heptane : ethyl acetate 1 : 1), HPLC-MS 206.0 $[\text{M} + \text{H}]^+$, 228.1 $[\text{M} + \text{Na}]^+$, 433.0 $[2\text{M} + \text{Na}]^+$.

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ii) 3-Phenyloxaziridine-2-carboxylic acid allyl ester (prepared as above, 1.16 g, 5.63 mmol) was added to a stirred solution of (S)-2-aminomethyl-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (96) (0.35 g, 1.50 mmol) in dichloromethane (10 ml). The mixture was stirred for 16 hours then the solvents
30 were removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 9 to 1 : 4 to give (S)-2-(N'-allyloxycarbonylhydrazinomethyl)-2,5-dihydropyrrole-1-carboxylic acid benzyl

-431-

ester (97) as a pale yellow oil (0.18 g, 36%). TLC (R_f = 0.45, heptane : ethyl acetate 1 : 1), analytical HPLC R_t = 14.789 min, HPLC-MS 332.1 $[M + H]^+$, 354.1 $[M + Na]^+$, 685.2 $[2M + Na]^+$. d_H (500 MHz, $CDCl_3$) mixture of rotamers, tentative assignment of spectrum 2.73-3.40 (2H, m, CH_2NHNH), 4.08-4.80 (5H, m, H-2, H-5 and $CH_2CH=CH_2$), 4.95-5.35 (4H, m, $PhCH_2O$ and $CH_2CH=CH_2$), 5.57-5.98 (3H, m, H-4, H-5 and $CH_2CH=CH_2$), 7.25-7.55 (5H, aromatics); d_C (125 MHz, $CDCl_3$) 53.61, 53.65, 54.02 and 54.07 (C-5 and CH_2NHNH), 65.24 (C-2), 65.87, 66.21, 66.43, 66.82 and 67.13 ($CH_2CH=CH_2$ and $PhCH_2O$), 117.48, 117.83, 118.20 and 118.49 ($CH_2CH=CH_2$), 127.00, 127.13, 127.70, 127.79, 127.93, 128.02, 128.13, 128.33, 128.52 and 128.54 (C-3, C-4 and aromatic CH), 132.11, 132.17, 132.21, 132.46, 132.54 and 132.68 ($CH_2CH=CH_2$), 136.65 (aromatic quaternary), 154.52, 154.82, 155.85 and 156.21 ($NNHC=O$), 158.69 ($CH_2NC=O$).

15 Preparation of (S)-2-(N-tert-butoxycarbonyl-N'-allyloxycarbonylhydrazinomethyl)-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (98)

Three portions of Boc anhydride (each 1.20 g, 5.55 mmol) were added at one hour intervals to a stirred solution of (S)-2-(N'-allyloxycarbonylhydrazinomethyl)-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (97) (184 mg, 0.56 mmol) in triethylamine : methanol (1 : 9, 10 ml). The mixture was stirred at 60 °C for 3 hours then the solvents were removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 9 to 1 : 4 to give (S)-2-(N-tert-butoxycarbonyl-N'-allyloxycarbonylhydrazinomethyl)-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (98) as a pale yellow oil (190 mg, 79%). TLC (R_f = 0.5, heptane : ethyl acetate 1 : 1), analytical HPLC R_t = 19.828 min, HPLC-MS 432.2 $[M + H]^+$, 454.1 $[M + Na]^+$, 885.2 $[2M + Na]^+$. d_H (500 MHz, $CDCl_3$) mixture of rotamers approximately 4 : 1, 1.38-1.45 (9H, br. s, $C(CH_3)_3$), 3.45-3.74 (2H, m, CH_2NNH), 4.02-4.16 (1H, m, H-5), 4.24-4.38 (1H, m, H-5), 4.54-4.68 (2H, m, $CH_2CH=CH_2$), 4.72 (minor), 4.84 (major) (1H total, each br. s, H-2), 5.03-5.20 (2H, m, $PhCH_2O$), 5.18-5.34 (2H, m, $CH_2CH=CH_2$), 5.76 (1H, br. s, H-3), 5.79-5.85 (1H, m, H-4), 5.84-5.95 (1H, m, $CH_2CH=CH_2$),

-432-

7.28-7.40 (5H, aromatics); d_c (125 MHz, $CDCl_3$) 28.07 ($C(CH_3)_3$), 53.32 (CH_2NNH), 53.86 (C-5), 62.45 and 62.86 (C-2), 66.21 and 67.02 ($CH_2CH=CH_2$ and $PhCH_2O$), 81.03 and 81.43 ($C(CH_3)_3$), 117.97 and 118.26 ($CH_2CH=CH_2$), 126.63, 128.00, 128.47 and 128.68 (C-3, C-4 and aromatic CH), 132.22 and 132.42 ($CH_2CH=CH_2$), 136.48 (aromatic quaternary), 154.96 and 155.57 ($NHNHC=O$ and $CH_2NC=O$).

Preparation of (S)-2-(N-tert-butoxycarbonylhydrazinomethyl)-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (99)

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Tetrakis(triphenylphosphine)palladium(0) (10.2 mg, 0.0088 mmol) was added to a stirred solution of (S)-2-(N-tert-butoxycarbonyl-N'-allyloxycarbonylhydrazine methyl)-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (98) (190 mg, 0.44 mmol) in dichloromethane (10 ml) under an atmosphere of argon. Phenylsilane (0.109 ml, 0.88 mmol) was then added dropwise over two minutes. The solution was stirred for 1 hour then the solvents were removed *in vacuo*. The oily residue was purified by flash chromatography over silica eluting with heptane : *tert*-butyl methyl ether 9 : 1 to 0 : 1 mixtures to give (S)-2-(N-tert-butoxycarbonylhydrazinomethyl)-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (99) as a pale yellow oil (148 mg, 97%). TLC (R_f = 0.35, heptane : ethyl acetate 1 : 1), analytical HPLC R_t = 15.669 min, HPLC-MS 248.1 [$M + 2H - Boc$] $^+$, 292.1 [$M + 2H - Bu$] $^+$, 370.1 [$M + Na$] $^+$, 717.3 [$2M + Na$] $^+$. d_H (500 MHz, $CDCl_3$) 1.41-1.45 (9H, br. s, $C(CH_3)_3$), 1.45-1.70 (2H, br. s, NH_2), 3.53-3.95 (2H, m, CH_2NNH_2), 4.03-4.12 (1H, m, H-5), 4.25-4.36 (1H, m, H-5), 4.74-4.91 (1H, m, H-2), 5.04-5.26 (2H, m, $PhCH_2O$), 5.73-5.87 (2H, m, H-4 and H-5), 7.28-7.41 (5H, aromatics); d_c (125 MHz, $CDCl_3$) 28.26 ($C(CH_3)_3$), 53.23 (C-5), 53.70 (CH_2NNH_2), 63.24 (C-2), 66.73 and 67.18 ($PhCH_2O$), 80.25 and 80.53 ($C(CH_3)_3$), 126.01, 127.82, 127.91, 128.08, 128.22, 128.42 and 128.49 (C-3 C-4, and aromatic CH), 136.69 (aromatic quaternary).

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-433-

Preparation of (2*S*)-2-[*N'*-((2*S*)-2-allyloxycarbonylamino-4-methylpentanoyl)-*N*-*tert*-butoxycarbonylhydrazinomethyl]-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (100)

5 (i) Preparation of Alloc-L-Leucine Fluoride (Alloc-Leu-F)

Alloc-L-Leucine (0.90 g, 4.2 mmol) was dissolved in dichloromethane (50 ml) with stirring under nitrogen. (Diethylamino)sulfur trifluoride (DAST, 790 μ l, 6.0 mmol) was added and the mixture stirred for 1.75 hours. The mixture was added
10 to iced-water (200 ml) and product extracted into dichloromethane (50 ml), dried (MgSO_4), and reduced *in vacuo* to a mobile tan oil (0.70 g, 77%). An analytical sample, pre-treated with 10% pyridine in methanol gave HPLC-MS 230.1 [$\text{M} + \text{H}$]⁺, 481.1 [$2\text{M} + \text{Na}$]⁺ (methyl ester).

15 (ii) Alloc-Leu-F (prepared as above, 47 mg, 0.21 mmol) was dissolved in dimethylformamide (1.5 ml) then added to (2*S*)-2-(*N*-*tert*-butoxycarbonyl-1-hydrazinomethyl)-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (99) (71 mg, 0.20 mmol) under an atmosphere of nitrogen. The solution was stirred for 19 hours then the solvents were removed *in vacuo*. The residue was purified by flash
20 chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 9 to 3 : 7 to give (2*S*)-2-[*N'*-((2*S*)-2-allyloxycarbonylamino-4-methylpentanoyl)-*N*-*tert*-butoxycarbonylhydrazinomethyl]-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (100) as a sticky white solid (69 mg, 63%). TLC (Single spot, $R_f = 0.75$, EtOAc : heptane 2 : 1), analytical HPLC broad double peak $R_t = 21.214$ and
25 21.483 min; HPLC-MS 445.2 [$\text{M} + 2\text{H} - \text{Boc}$]⁺, 489.2 [$\text{M} + 2\text{H} - \text{Bu}$]⁺, 545.2 [$\text{M} + \text{H}$]⁺.

Preparation of (2*S*)-2-[*N'*-((2*S*)-2-amino-4-methylpentanoyl)-*N*-*tert*-butoxycarbonylhydrazinomethyl]-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (101)

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-434-

Dichloromethane (1.5 ml) followed by phenylsilane (32 μ l, 0.26 mmol) were consecutively added with stirring under an atmosphere of nitrogen to a mixture of tetrakis(triphenylphosphine) palladium(0) (3.0 mg, 0.003 mmol) and (2*S*)-2-[*N'*-((2*S*)-2-allyloxycarbonylamino-4-methylpentanoyl)-*N*-*tert*-butoxycarbonylhydrazinomethyl]-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (100) (70 mg, 0.129 mmol). The solution was stirred for 80 minutes then purified by flash chromatography over silica eluting with methanol : dichloromethane mixtures 0 : 100 to 5 : 95 to give (2*S*)-2-[*N'*-((2*S*)-2-amino-4-methylpentanoyl)-*N*-*tert*-butoxycarbonylhydrazinomethyl]-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (101) as a colourless oil (57 mg, 96%). TLC (Single spot, R_f = 0.65, MeOH : dichloromethane 1 : 9), analytical HPLC R_t = 16.345 min; HPLC-MS 461.2 [M + H]⁺, 483.2 [M + Na]⁺, 921.4 [2M + H]⁺.

Preparation of (2*S*)-2-{*N*-*tert*-butoxycarbonyl-*N'*-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-hydrazinoymethyl}-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (102)

4-Methylmorpholine (26.6 μ l, 0.244 mmol) was added to a solution of HBTU (46 mg, 0.122 mmol), 1-hydroxybenzotriazole monohydrate (18.6 mg, 0.122 mmol) and 4-(*tert*-butyl)benzoic acid (22 mg, 0.122 mmol) in dimethylformamide (1.5 ml). The solution was stood for 5 minutes then added to (2*S*)-2-[*N'*-((2*S*)-2-amino-4-methylpentanoyl)-*N*-*tert*-butoxycarbonylhydrazinomethyl]-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (101) (56 mg, 0.122 mmol). The mixture was stirred for 1 hour then the solvents were removed *in vacuo* (water bath temperature < 33 °C). The residue was dissolved in dichloromethane (15 ml) then washed with pH 3 hydrochloric acid (5 ml), saturated aqueous sodium hydrogen carbonate solution (5 ml) and brine (5 ml), dried (Na₂SO₄), and the solvents removed *in vacuo*. The yellow residue (108 mg) was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 9 to 3 : 7 to give (2*S*)-2-{*N*-*tert*-butoxycarbonyl-*N'*-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-hydrazinoymethyl}-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (102) as a sticky white solid (63 mg, 84%). TLC (R_f = 0.55, EtOAc :

-435-

heptane 1 : 1), analytical HPLC $R_t = 24.205$ min; HPLC-MS 521.2 $[M + 2H - Boc]^+$, 621.3 $[M + H]^+$.

Preparation of (2*S*)-2-{*N*-*tert*-butoxycarbonyl-*N'*-[(2*S*)-2-(4-*tert*-butylbenzoyl)amino]-4-methylpentanoyl]-hydrazinomethyl}-6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (103)

A solution of *meta*-chloroperoxybenzoic acid (57-86%, 196 mg, ~0.81 mmol) in dichloromethane (1.2 ml) was added to (2*S*)-2-{*N*-*tert*-butoxycarbonyl-*N'*-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-hydrazinoylmethyl}-2,5-dihydropyrrole -1-carboxylic acid benzyl ester (102) (50 mg, 0.081 mmol) under an atmosphere of nitrogen. The solution was stirred for 20 hours then dichloromethane (15 ml) was added and the mixture washed with 5% aqueous sodium hydroxide solution (10 ml), then 10% aqueous sodium hydroxide solution (5 ml), dried (Na_2SO_4), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 40 : 60 to give (2*S*)-2-{*N*-*tert*-butoxycarbonyl-*N'*-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-hydrazino methyl}-6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (103) as a white solid (39 mg, 75%). TLC ($R_f = 0.30$, EtOAc : heptane 2 : 3), analytical HPLC $R_t = 23.156$ min; HPLC-MS 537.2 $[M + 2H - Boc]^+$, 637.2 $[M + H]^+$.

Preparation of (3*aR*, 6*S*, 6*aS*)-1-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2,4-dicarboxylic acid 4-benzyl ester 2-*tert*-butyl ester (104)

A solution of (2*S*)-2-{*N*-*tert*-butoxycarbonyl-*N'*-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-hydrazinomethyl}-6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (103) (38.5 mg, 0.061 mmol) in acetonitrile (4.0 ml) was added to potassium carbonate (210 mg, 1.51 mmol). The suspension was placed under an atmosphere of nitrogen then heated at 60 °C whilst stirring for 4.75 hours before being allowed to cool to ambient temperature. The

-436-

suspension was filtered then the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 50 : 50 to give (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]

5 pyrazole-2,4-dicarboxylic acid 4-benzyl ester 2-*tert*-butyl ester (104) as a white solid (16.2 mg, 42%). TLC (R_f = 0.30, EtOAc : heptane 1 : 1), analytical HPLC R_t = 21.762 min; HPLC-MS 537.2 $[M + 2H - Boc]^+$, 581.1 $[M + 2H - Bu]^+$, 637.2 $[M + H]^+$.

10 **Preparation of (3aR, 6S, 6aS)-4-benzoyl-1-[(2S)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (106)**

Under an atmosphere of nitrogen a solution of (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]
15 pyrazole-2,4-dicarboxylic acid 4-benzyl ester 2-*tert*-butyl ester (104) (16.0 mg, 0.025 mmol) in ethanol (1.5 ml) was added to 10% palladium on charcoal (10 mg) whilst stirring. The nitrogen was replaced by hydrogen then stirring continued for 30 minutes. The hydrogen was replaced by nitrogen then the mixture filtered
20 through celite. The filter cake was washed with ethanol (40 ml) then the filtrate concentrated *in vacuo*. The residue was used without further purification. Analytical HPLC R_t = 18.568 min; HPLC-MS 403.2 $[M + 2H - Boc]^+$, 503.2 $[M + H]^+$ for (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*] pyrazole-2-carboxylic acid *tert*-butyl ester
25 (105).

Benzoic anhydride (6.0 mg, 0.026 mmol), dimethylformamide (0.3 ml) then 4-methylmorpholine (5.8 μ l, 0.053 mmol) were added consecutively to (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-hydroxyhexa
30 hydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (105) (~0.025 mmol, prepared as above). The solution was stirred for 65 minutes then the majority of solvents were removed *in vacuo*. The residue was dissolved in ethyl

-437-

acetate (10 ml), then washed with saturated aqueous sodium hydrogen carbonate solution (5 ml), pH 3 hydrochloric acid (5 ml) and brine (5 ml), dried (Na₂SO₄), and the solvents removed *in vacuo*. The residue (15.5 mg) was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 5 : 95 to 50 : 50 to give (3a*R*, 6*S*, 6a*S*)-4-benzoyl-1-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (106) as a white solid (10.3 mg, 68%). TLC (*R_f* = 0.25, EtOAc : heptane 1 : 1), analytical HPLC *R_t* = 22.101 min; HPLC-MS 278.1, 507.2 [M + 2H - Boc]⁺, 607.2 [M + H]⁺.

Preparation of (3a*R*, 6a*S*)-4-benzoyl-1-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-oxo-hexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (107)

A solution of Dess-Martin periodinane (54 mg, 0.128 mmol) in dichloromethane (1.25 ml) was added to (3a*R*, 6*S*, 6a*S*)-4-benzoyl-1-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (106) (15.5 mg, 0.026 mmol) under an atmosphere of nitrogen. The mixture was stirred for 4.5 hours then purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 9 to 2 : 3 to give (3a*R*, 6a*S*)-4-benzoyl-1-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-oxo-hexahydro pyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (107) as a white solid (12.8 mg, 81%). TLC (*R_f* = 0.65, EtOAc : heptane 3 : 2), analytical HPLC broad peak *R_t* = 21.02-23.60 min; HPLC-MS single broad main UV peak 274.1, 505.2 [M + 2H - Boc]⁺, 549.1 [M + 2H - Bu]⁺, 605.2 [M + H]⁺, 623.2 [M + H₂O + H]⁺, 627.2 [M + Na]⁺, 645.2 [M + H₂O + Na]⁺.

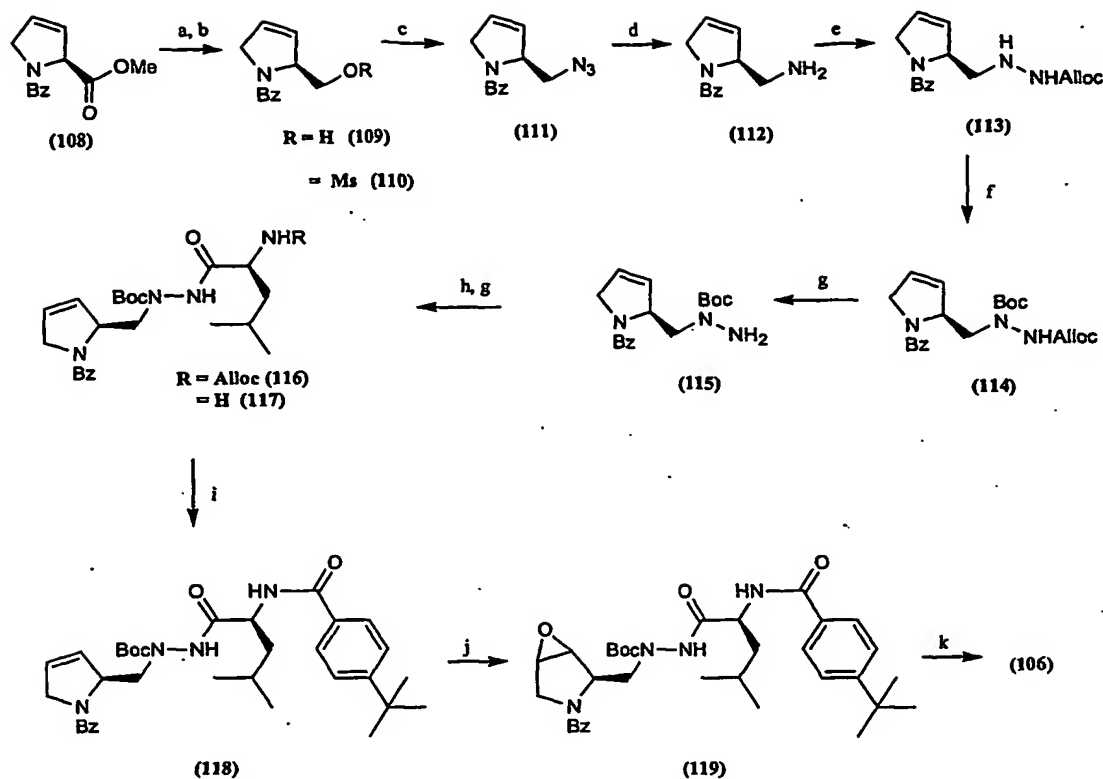
Preparation of (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*c*] pyrazole-1-carbonyl)-3-methylbutyl]-4-*tert*-butylbenzamide (EXAMPLE 249a)

-438-

Trifluoroacetic acid (0.15 ml) was added to (3aR, 6aS)-4-benzoyl-1-[(2S)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-oxo-hexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (107) (10.3 mg, 0.017 mmol) under an atmosphere of nitrogen. The solution was stirred for 45 minutes then cautiously
5 added to saturated aqueous sodium hydrogen carbonate solution (10 ml). The product was extracted into dichloromethane (10 ml) then washed with water (10 ml), dried (Na₂SO₄), and the solvents removed *in vacuo*. The residue (10 mg) was combined with a second batch of material (0.8 mg, prepared in a similar way to above from 1.14 mg of (3aR, 6aS)-4-benzoyl-1-[(2S)-2-(4-*tert*-butyl
10 benzoylamino)-4-methylpentanoyl]-6-oxo-hexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (107), then purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 20 : 80 to 65 : 35 to give (3aR, 6aS)-*N*-[(1S)-1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*c*]pyrazole-1-carbonyl)-3-methylbutyl]-4-*tert*-butylbenzamide (EXAMPLE 249a) as an off-white solid (3.49
15 mg, 37 %), together with recovered (3aR, 6aS)-4-benzoyl-1-[(2S)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-oxo-hexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (107) (1.83 mg, 16%). Data for (3aR, 6aS)-*N*-[(1S)-1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*c*]pyrazole-1-carbonyl)-3-methylbutyl]-4-*tert*-butylbenzamide (EXAMPLE 249a), TLC (*R_f* = 0.26, EtOAc :
20 heptane 3 : 1), analytical HPLC broad peak *R_t* = 18.10-19.70 min; HPLC-MS single broad main UV peak 274.1, 505.1 [M + H]⁺, 523.2 [M + H₂O + H]⁺.

An alternative preparation of (3aR, 6S, 6aS)-4-benzoyl-1-[(2S)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (106) is detailed in Scheme 24.
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-439-



Scheme 24. (a) LiBH_4 , MeOH, THF (b) Methanesulfonyl chloride, triethylamine, DCM (c) Sodium azide, DMF, 110°C (d) Ph_3P / H_2O , 1,4-dioxane, 50°C (e) 3-Phenyloxaziridine-2-carboxylic acid allyl ester, DCM (f) $(\text{Boc})_2\text{O}$, DCM, 60°C (g) $\text{Pd}(\text{PPh}_3)_4$, PhSiH_3 , DCM (h) Alloc-Leu-F, DMF (i) 4-*tert*-Butylbenzoic acid, HBTU, HOBT, NMM, DMF (j) *m*-Chloroperoxybenzoic acid, DCM. (k) Potassium carbonate, CH_3CN , 60°C

10 Preparation of (S)-1-benzoyl-2,5-dihydro-1H-pyrrole-2-carboxylic acid 1-methyl ester (108)

Benzoic anhydride (4.15 g, 18.3 mmol) followed by 4-methylmorpholine (2.82 ml, 25.7 mmol) were consecutively added to a stirred solution of (S)-2,5-dihydro-1H-pyrrole-2-carboxylic acid methyl ester hydrochloride (2.0 g, 12.2 mmol) in DMF (50 ml). The mixture was stirred for 1.5 hours then the solvents were removed *in vacuo*. The product was extracted into *tert*-butyl methyl ether (300 ml) then washed with 5% hydrochloric acid (100 ml), 5% aqueous sodium hydrogen carbonate solution (100 ml), and brine (100 ml), dried (MgSO_4), and the solvents

-440-

removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane 1 : 4 to give (*S*)-1-benzoyl-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid 1-methyl ester (**108**) as a colourless oil (2.05 g, 73%). TLC (R_f = 0.25, EtOAc : heptane 1 : 1); HPLC-MS 232.1, $[M + H]^+$, 254.0 $[M + Na]^+$, 485.1 $[2M + Na]^+$; δ_H (500 MHz, $CDCl_3$) 3.78 (3H, s, OCH_3), 4.15-4.22 (1H, m, H-5), 4.41-4.47 (1H, m, H-5), 5.45-5.49 (1H, m, H-2), 5.83-5.95 (2H, m, H-3 and H-4), 7.36-7.58 (5H, aromatics); δ_C (125 MHz, $CDCl_3$) 52.50 (OCH_3), 55.90 (C-5), 66.39 (C-2), 124.89, 127.01, 128.39, 128.41, 128.60 and 130.24 (C-3, C-4 and aromatic \underline{CH}), 135.86 (aromatic quaternary), 169.73 and 170.16 ($CHC=O$ and $NC=OPh$).

Preparation of (*S*)-(2-hydroxymethyl-2,5-dihydropyrrole-1-yl)phenylmethanone (109**)**

Methanol (0.71 ml) followed by a solution of (*S*)-1-benzoyl-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid 1-methyl ester (**108**) (2.05 g, 8.9 mmol) in THF (37 ml) were added dropwise to a stirred suspension of lithium borohydride (390 mg, 17.7 mmol) in THF (13 ml). The mixture was stirred for 1 hour then water (5 ml) was carefully added. The product was extracted into *tert*-butyl methyl ether (3 x 50 ml), then the combined organic layers dried ($MgSO_4$), and the solvents removed *in vacuo* to give (*S*)-(2-hydroxymethyl-2,5-dihydropyrrole-1-yl)phenylmethanone (**109**) as a pale yellow oil (1.68 g, 93%) which was used without further purification. TLC (R_f = 0.1, EtOAc : heptane 1 : 1), HPLC-MS 204.1 $[M + H]^+$; δ_H (500 MHz, $CDCl_3$) 1.65-1.95 (1H, br. s, CH_2OH), 3.72 (1H, dd J = 11.4 and 7.1 Hz, CH_2OH), 3.90 (1H, dd J = 11.6 and 2.1 Hz, CH_2OH), 4.11-4.16 (1H, m, H-5), 4.27-4.38 (1H, m, H-5), 5.17-5.21 (1H, m, H-2), 5.74-5.82 (2H, m, H-3 and H-4), 7.38-7.53 (5H, aromatics); δ_C (125 MHz, $CDCl_3$) 56.76 (C-5), 66.44 ($\underline{CH_2OH}$), 68.68 (C-2), 126.25, 126.67, 126.93, 126.95, 128.50 and 130.20 (C-3, C-4 and aromatic \underline{CH}), 136.21 (aromatic quaternary), 172.12 ($NC=OPh$).

Preparation of (*S*)-methanesulfonic acid 1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl ester (110**)**

-441-

Triethylamine (1.86 ml, 13.2 mmol) was added dropwise to a stirred solution of (*S*)-(2-hydroxymethyl-2,5-dihydropyrrole-1-yl)phenylmethanone (109) (1.68 g, 8.3 mmol) and methanesulfonyl chloride (0.96 ml, 12.4 mmol) in dichloromethane (30 ml) at 0 °C. The mixture was stirred for 30 minutes at ambient temperature then washed with water (100 ml), and brine (100 ml), dried (Na_2SO_4), and the solvents removed *in vacuo* to give (*S*)-methanesulfonic acid 1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl ester (110) as a pale yellow oil (1.88 g, 81%) which was used without further purification. HPLC-MS 282.0 $[\text{M} + \text{H}]^+$, 585.1 $[\text{2M} + \text{Na}]^+$.

Preparation of (*S*)-(2-azidomethyl-2,5-dihydropyrrol-1-yl)phenylmethanone (111)

Sodium azide (2.17 g, 33.4 mmol) was added to a stirred solution of (*S*)-methanesulfonic acid 1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl ester (110) (1.88 g, 6.68 mmol) in DMF (50 ml). The reaction mixture was stirred at 110 °C for 1 hour. The solvent was removed *in vacuo* then the product was extracted into ethyl acetate (100 ml), washed with water (100 ml) and brine (100 ml), dried (MgSO_4), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with heptane : ethyl acetate 9 : 1 to give (*S*)-(2-azidomethyl-2,5-dihydropyrrol-1-yl)phenylmethanone (111) as a pale yellow oil (0.96 g, 63%). TLC (R_f = 0.40, heptane : ethyl acetate 1 : 1), analytical HPLC R_t = 13.943 min, HPLC-MS 229.1 $[\text{M} + \text{H}]^+$, 251.1 $[\text{M} + \text{Na}]^+$, 479.1 $[\text{2M} + \text{Na}]^+$.

Preparation of (*S*)-(2-aminomethyl-2,5-dihydro-pyrrol-1-yl)phenyl methanone (112)

Triphenylphosphine (1.65 g, 6.30 mmol) was added to a stirred solution of (*S*)-(2-azidomethyl-2,5-dihydropyrrol-1-yl)phenylmethanone (111) (0.96 g, 4.2 mmol) in THF (87 ml) containing water (1 ml). The mixture was stirred at 50 °C for 24 hours then the solvents were removed *in vacuo*. The residue was purified by flash

-442-

chromatography over silica eluting with ethyl acetate : heptane 1 : 9 then ethyl acetate : methanol 4 : 1 mixtures to give (*S*)-(2-aminomethyl-2,5-dihydro-pyrrol-1-yl)phenylmethanone (**112**) as a pale yellow oil (0.77 g, 91%). TLC (R_f = 0.1, chloroform : methanol 9 : 1), analytical HPLC with UV peaks at R_t = 6.705 and 7.943 min; HPLC-MS 203.1 $[M + H]^+$, 427.1 $[2M + Na]^+$. d_H (500 MHz, D_6 -DMSO) 1.30-2.10 (2H, br. s, CH_2NH_2), 2.84 (2H, m, CH_2NH_2), 3.87 (1H, dd, J = 14.9 and 1.0 Hz, H-5), 4.26-4.35 (1H, m, H-5), 4.84 (1H, m, H-2), 5.83-6.03 (2H, m, H-4 and H-5), 7.39-7.58 (5H, aromatics); d_C (125 MHz, D_6 -DMSO) 44.25 (CH_2NH_2), 56.96 (C-5), 67.20 (C-2), 126.50, 126.62, 126.83, 127.51, 128.63, 128.84, 128.96, 129.52, 129.81 and 130.22 (C-3, C-4 and aromatic \underline{CH}), 137.48 (aromatic quaternary), 169.44 ($NC=O$).

Preparation of (*S*)-*N*-(1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)hydrazine carboxylic acid allyl ester (113**)**

3-Phenyloxaziridine-2-carboxylic acid allyl ester (prepared as above, 1.95 g, 9.5 mmol) was added to a stirred solution of (*S*)-(2-aminomethyl-2,5-dihydro-pyrrol-1-yl)phenylmethanone (**112**) (0.64 g, 3.17 mmol) in dichloromethane (10 ml). The mixture was stirred for 16 hours then the solvents were removed *in vacuo*. The oily residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 9 to 1 : 4 to give (*S*)-*N*-(1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)hydrazinecarboxylic acid allyl ester (**113**) as a pale yellow oil (0.26 g, 27%). TLC (R_f = 0.45, heptane : ethyl acetate 1 : 1), HPLC-MS 302.1 $[M + H]^+$, 324.1 $[M + Na]^+$, 625.1 $[2M + Na]^+$.

Preparation of (*S*)-*N'*-(1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)-*N'*-tert-butoxycarbonylhydrazinecarboxylic acid allyl ester (114**)**

Three portions of Boc anhydride (each 1.84 g, 8.1 mmol) were added at one hour intervals to a stirred solution of (*S*)-*N*-(1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)hydrazinecarboxylic acid allyl ester (**113**) (0.26 g, 0.85 mmol) in triethylamine : methanol (1 : 9, 10 ml). The mixture was stirred at 60 °C for 3

-443-

hours then the solvents were removed *in vacuo*. The oily residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 1 to 1 : 4 to give (*S*)-*N*-(1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)-*N'*-*tert*-butoxycarbonyl-hydrazinecarboxylic acid allyl ester (**114**) as a pale yellow oil (96 mg, 28%). TLC (R_f = 0.25, heptane : ethyl acetate 1 : 1), analytical HPLC R_t = 6.025 min; HPLC-MS 402.1 $[M + H]^+$, 825.1 $[2M + Na]^+$.

Preparation of (*S*)-*N*-(1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)hydrazine carboxylic acid *tert*-butyl ester (115**)**

Tetrakis(triphenylphosphine)palladium(0) (7.5 mg, 0.0065mmol) was added to a stirred solution of (*S*)-*N*-(1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)-*N'*-*tert*-butoxycarbonyl-hydrazinecarboxylic acid allyl ester (**114**) (131 mg, 0.326 mmol) in dichloromethane (5 ml) under an atmosphere of argon. Phenylsilane (81 μ l, 0.65 mmol) was then added dropwise over two minutes. The solution was stirred for 1 hour then the solvents were removed *in vacuo*. The oily residue was purified by flash chromatography over silica eluting with heptane : *tert*-butyl methyl ether 9 : 1 to 0 : 1 mixtures to give (*S*)-*N*-(1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)hydrazine carboxylic acid *tert*-butyl ester (**115**) as a brown oil (77 mg, 74%). TLC (R_f = 0.35, heptane : ethyl acetate 1 : 1), analytical HPLC R_t = 12.738 min; HPLC-MS 218.1 $[M + 2H - Boc]^+$, 262.1 $[M + 2H - Bu]^+$, 318.1 $[M + H]^+$, 635.3 $[2M + H]^+$, 657.2 $[2M + Na]^+$.

Preparation of *N'*-((2*S*)-2-allyloxycarbonylamino-4-methylpentanoyl)-*N*-((2*S*)-1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)hydrazinecarboxylic acid *tert*-butyl ester (116**)**

Alloc-Leu-F (prepared as above, 55 mg, 0.26 mmol) was added to a stirred solution of (*S*)-2-*N*-(1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)hydrazine carboxylic acid *tert*-butyl ester (**115**) (77 mg, 0.24 mmol) in dimethylformamide (1.5 ml) under an atmosphere of nitrogen. The solution was stirred for 4.5 hours then the solvents were removed *in vacuo*. The residue was purified by flash

-444-

chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 9 to 2 : 3 to give *N'*-((2*S*)-2-allyloxycarbonylamino-4-methylpentanoyl)-*N*-((2*S*)-1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)hydrazinecarboxylic acid *tert*-butyl ester (116) as a viscous oil (83 mg, 67%). TLC (Single spot, R_f = 0.45, EtOAc : heptane 1 : 1), analytical HPLC R_t = 19.157 min; HPLC-MS 415.1 [M + 2H - Boc]⁺, 459.1 [M + 2H - Bu]⁺, 515.2 [M + H]⁺.

Preparation of *N'*-((2*S*)-2-amino-4-methylpentanoyl)-*N*-((2*S*)-1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)hydrazinecarboxylic acid *tert*-butyl ester (117)

10

Dichloromethane (1.5 ml) followed by phenylsilane (39 μ l, 0.32 mmol) were consecutively added with stirring under an atmosphere of nitrogen to a mixture of tetrakis(triphenylphosphine) palladium(0) (3.7 mg, 0.003 mmol) and *N'*-((2*S*)-2-allyloxycarbonylamino-4-methylpentanoyl)-*N*-((2*S*)-1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)hydrazinecarboxylic acid *tert*-butyl ester (116) (82 mg, 0.16 mmol). The solution was stirred for 1.75 hours then purified by flash chromatography over silica eluting with methanol : dichloromethane mixtures 1 : 99 to 5 : 95 to give *N'*-((2*S*)-2-amino-4-methylpentanoyl)-*N*-((2*S*)-1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl) hydrazinecarboxylic acid *tert*-butyl ester (117) as a colourless oil (57 mg, 83%). TLC (Single spot, R_f = 0.45, MeOH : dichloromethane 6 : 94), analytical HPLC R_t = 14.217 min; HPLC-MS 431.1 [M + H]⁺, 861.3 [2M + H]⁺, 883.3 [2M + Na]⁺.

20

Preparation of *N*-((2*S*)-1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)-*N'*-((2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl)hydrazinecarboxylic acid *tert*-butyl ester (118)

25

4-Methylmorpholine (28.5 μ l, 0.26 mmol) was added to a solution of HBTU (49 mg, 0.13 mmol), 1-hydroxybenzotriazole monohydrate (20 mg, 0.13 mmol) and 4-(*tert*-butyl)benzoic acid (23 mg, 0.13 mmol) in dimethylformamide (1.5 ml). The solution was stood for 5 minutes then added to *N'*-((2*S*)-2-amino-4-methylpentanoyl)-*N*-((2*S*)-1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)

30

-445-

hydrazine carboxylic acid *tert*-butyl ester (117) (56 mg, 0.13 mmol). The mixture was stirred for 1.5 hour then the solvents were removed *in vacuo* (water bath temperature < 33 °C). The residue was dissolved in dichloromethane (15 ml) then washed with pH 3 hydrochloric acid (5 ml), saturated aqueous sodium hydrogen carbonate solution (5 ml) and brine (5 ml), dried (Na₂SO₄), and the solvents removed *in vacuo*. The yellow residue (102 mg) was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 9 to 1 : 1 to give *N*-((2*S*)-1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)-*N'*-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]hydrazinecarboxylic acid *tert*-butyl ester (118) as a white solid (52 mg, 68%). TLC (*R*_f = 0.46, EtOAc : heptane 1 : 1), analytical HPLC *R*_t = 22.310 min; HPLC-MS 491.2 [M + 2H - Boc]⁺, 591.2 [M + H]⁺.

Preparation of *N*-((2*S*)-3-benzoyl-6-oxa-3-aza-bicyclo[3.1.0]hex-2-ylmethyl)-*N'*-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]hydrazine carboxylic acid *tert*-butyl ester (119)

A solution of *meta*-chloroperoxybenzoic acid (57-86%, 210 mg, ~0.86 mmol) in dichloromethane (1.25 ml) was added to *N*-((2*S*)-1-benzoyl-2,5-dihydro-1*H*-pyrrol-2-ylmethyl)-*N'*-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]hydrazine carboxylic acid *tert*-butyl ester (118) (51 mg, 0.086 mmol) under an atmosphere of nitrogen. The solution was stirred for 20 hours then dichloromethane (15 ml) was added and the mixture washed with 10% aqueous sodium hydroxide solution (10 ml). The aqueous layer was extracted with dichloromethane (5 ml) then the combined organic layers washed with 10% aqueous sodium hydroxide solution (10 ml), dried (Na₂SO₄), and the solvents removed *in vacuo*. The yellow oily residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 9 to 1 : 1 to give *N*-((2*S*)-3-benzoyl-6-oxa-3-aza-bicyclo[3.1.0]hex-2-ylmethyl)-*N'*-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]hydrazinecarboxylic acid *tert*-butyl ester (119) as a white solid (27.5 mg, 52%). TLC (*R*_f = 0.25, EtOAc : heptane 1 : 1),

-446-

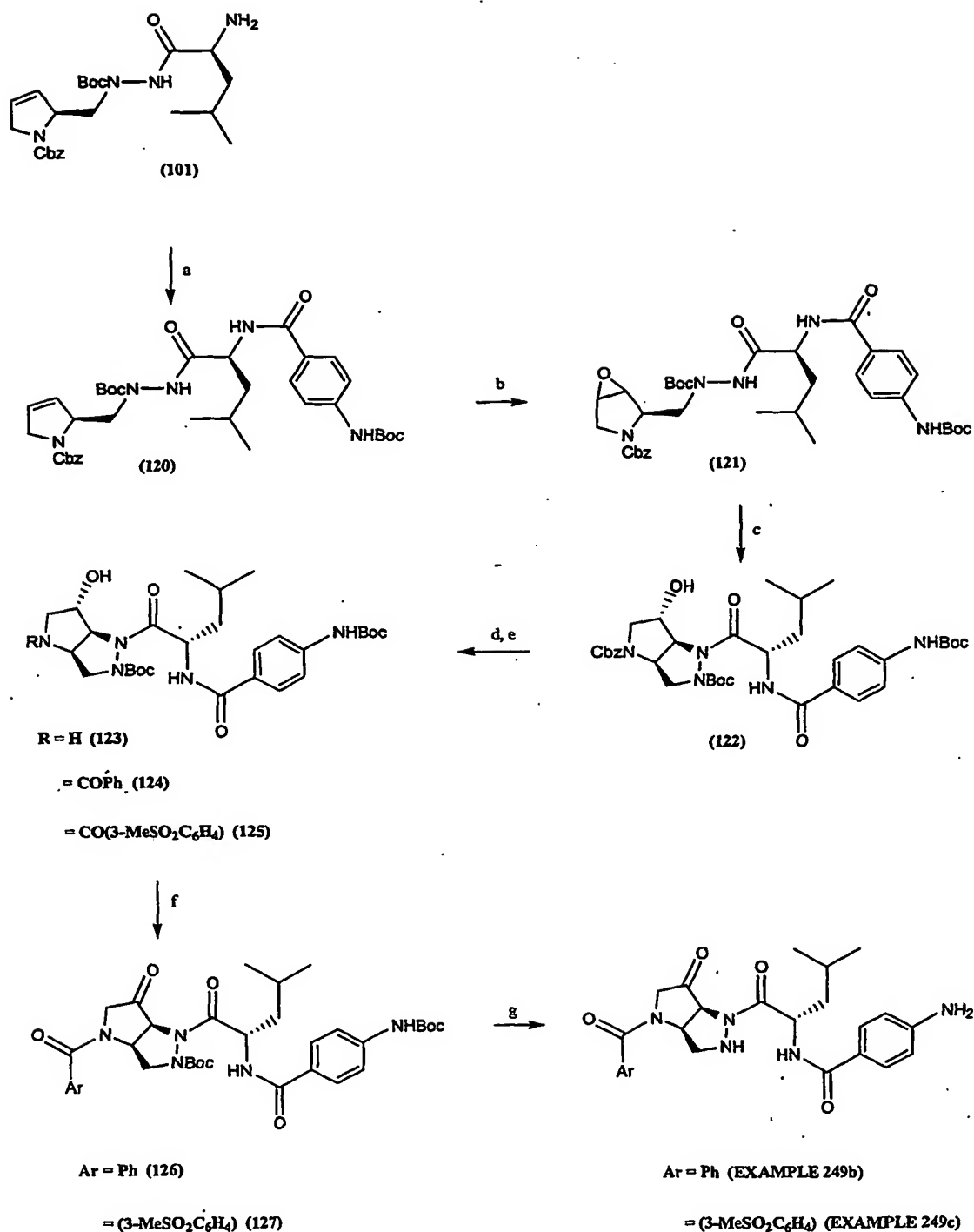
analytical HPLC R_t = 21.769 min; HPLC-MS 507.2 $[M + 2H - Boc]^+$, 607.2 $[M + H]^+$.

Preparation of (3aR, 6S, 6aS)-4-benzoyl-1-[(2S)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (106)

A solution of *N*-((2S)-3-benzoyl-6-oxa-3-aza-bicyclo[3.1.0]hex-2-ylmethyl)-*N'*-[(2S)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]hydrazinecarboxylic acid *tert*-butyl ester (119) (26 mg, 0.043 mmol) in acetonitrile (2.5 ml) was added to potassium carbonate (150 mg, 1.09 mmol). The suspension was placed under an atmosphere of nitrogen then heated at 60 °C whilst stirring for 3.25 hours before being allowed to cool to ambient temperature. The suspension was filtered and the collected solid washed with acetonitrile (20 ml), then the filtrate was concentrated *in vacuo*. The residue was dissolved in dichloromethane (15 ml), washed with water (10 ml), dried (Na_2SO_4), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 4 to 1 : 1 to give (3aR, 6S, 6aS)-4-benzoyl-1-[(2S)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (106) as a white solid (16.2 mg, 62%). TLC (R_f = 0.30, EtOAc : heptane 3 : 2), analytical HPLC R_t = 22.013 min; HPLC-MS 278.1, 507.2 $[M + 2H - Boc]^+$, 607.2 $[M + H]^+$.

EXAMPLES 249b and 249c were prepared from the intermediate (2S)-2-[*N'*-((2S)-2-amino-4-methylpentanoyl)-*N*-*tert*-butoxycarbonylhydrazinomethyl]-2,5-dihydro pyrrole-1-carboxylic acid benzyl ester (101) following Scheme 25;

-447-



5 Scheme 25. (a) 4-*tert*-Butoxycarbonylamino

benzoic acid, HBTU, HOBT, NMM, DMF (b) *m*-Chloroperoxybenzoic acid, DCM. (c) Potassium carbonate, CH₃CN, 60°C (d) Pd-C, H₂, ethanol (e) (PhCO)₂O, DMF or HBTU, HOBT, NMM, DMF, 3-(methylsulfonyl)benzoic acid (f) Dess-Martin periodinane, DCM (g) TFA, DCM

-448-

Preparation of (2S)-2-{N-tert-butoxycarbonyl-N'-[(2S)-2-(4-tert-butoxycarbonylamino)benzoylamino]-4-methylpentanoyl]-hydrazinoyl methyl}-2,5-dihydro pyrrole-1-carboxylic acid benzyl ester (120)

5 4-Methylmorpholine (44.7 μ l, 0.407 mmol) was added to a solution of HBTU (77 mg, 0.204 mmol), 1-hydroxybenzotriazole monohydrate (31 mg, 0.204 mmol) and 4-(tert-butoxycarbonylamino)benzoic acid (48 mg, 0.204 mmol) in dimethylformamide (2.0 ml). The solution was stood for 5 minutes then added to

10 (2S)-2-[N'-((2S)-2-amino-4-methylpentanoyl)-N-tert-butoxycarbonylhydrazino methyl]-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (101) (94 mg, 0.204 mmol). The mixture was stirred for 1 hour 35 minutes then the solvents were removed *in vacuo* (water bath temperature < 37 °C). The residue was dissolved in dichloromethane (15 ml) then washed with pH 3 hydrochloric acid (5 ml),

15 saturated aqueous sodium hydrogen carbonate solution (5 ml) and brine (5 ml), dried (Na₂SO₄), and the solvents removed *in vacuo*. The residue (166 mg) was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 9 to 4 : 6 to give (2S)-2-{N-tert-butoxycarbonyl-N'-[(2S)-2-(4-tert-butoxycarbonylamino)benzoylamino]-4-methylpentanoyl]-hydrazinoylmethyl}-

20 2,5-dihydropyrrole-1-carboxylic acid benzyl ester (120) as a white solid (116 mg, 84%). TLC (R_f = 0.48, EtOAc : heptane 1 : 1), analytical HPLC R_t = 22.296 min; HPLC-MS 580.4 [M + 2H - Boc]⁺, 680.4 [M + H]⁺.

Preparation of (2S)-2-{N-tert-butoxycarbonyl-N'-[(2S)-2-(4-tert-butoxycarbonylamino)benzoylamino]-4-methylpentanoyl]-hydrazinomethyl}-6-oxa-3-aza-bicyclo [3.1.0]hexane-3-carboxylic acid benzyl ester (121)

A solution of *meta*-chloroperoxybenzoic acid (57-86%, 411 mg, ~1.7 mmol) in dichloromethane (2.5 ml) was added to (2S)-2-{N-tert-butoxycarbonyl-N'-[(2S)-2-(4-tert-butoxycarbonylamino)benzoylamino]-4-methylpentanoyl]-hydrazinoyl

30 methyl}-2,5-dihydropyrrole-1-carboxylic acid benzyl ester (120) (115 mg, 0.169 mmol) under an atmosphere of nitrogen. The solution was stirred for 20 hours

-449-

then dichloromethane (15 ml) was added and the solution twice washed with a mixture of water (5 ml) and aqueous saturated sodium hydrogen carbonate solution (5 ml), dried (Na_2SO_4), and the solvents removed *in vacuo*. The residue (127 mg) was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 9 to 1 : 1 to give (2*S*)-2-{*N*-*tert*-butoxycarbonyl-*N'*-[(2*S*)-2-(4-*tert*-butoxycarbonylaminobenzoylamino)-4-methylpentanoyl]-hydrazinomethyl}-6-oxa-3-aza-bicyclo[3.1.0] hexane-3-carboxylic acid benzyl ester (121) as a white solid (63.7 mg, 54%). TLC (R_f = 0.25, EtOAc : heptane 1 : 1), analytical HPLC R_t = 21.723 min; HPLC-MS 596.4 [$\text{M} + 2\text{H} - \text{Boc}$]⁺, 696.4 [$\text{M} + \text{H}$]⁺, 718.4 [$\text{M} + \text{Na}$]⁺.

Preparation of (3*aR*, 6*S*, 6*aS*)-1-[(2*S*)-2-(4-*tert*-butoxycarbonylamino benzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2,4-dicarboxylic acid 4-benzyl ester 2-*tert*-butyl ester (122)

A solution of (2*S*)-2-{*N*-*tert*-butoxycarbonyl-*N'*-[(2*S*)-2-(4-*tert*-butoxycarbonylaminobenzoylamino)-4-methylpentanoyl]-hydrazinomethyl}-6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid benzyl ester (121) (62.2 mg, 0.090 mmol) in acetonitrile (3.0 ml) was added to potassium carbonate (300 mg, 2.17 mmol). The suspension was placed under an atmosphere of nitrogen then heated at 60 °C whilst stirring for 3 hours before being allowed to cool to ambient temperature. The suspension was filtered then the filtrate concentrated *in vacuo*. The product was extracted into dichloromethane (15 ml) then washed with water (5 ml), dried (Na_2SO_4), and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 1 : 4 to 3 : 2 to give (3*aR*, 6*S*, 6*aS*)-1-[(2*S*)-2-(4-*tert*-butoxycarbonylamino benzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2,4-dicarboxylic acid 4-benzyl ester 2-*tert*-butyl ester (122) as a white solid (36.7 mg, 59%). TLC (R_f = 0.28, EtOAc : heptane 1 : 1), analytical HPLC R_t = 22.528 min; HPLC-MS 333.3, 596.4 [$\text{M} + 2\text{H} - \text{Boc}$]⁺, 640.4 [$\text{M} + 2\text{H} - \text{Bu}$]⁺, 696.4 [$\text{M} + \text{H}$]⁺.

-450-

Preparation of (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-butoxycarbonylamino benzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (123)

5 Under an atmosphere of nitrogen ethanol (2.6 ml) was added to a mixture of (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-butoxycarbonylamino benzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2,4-dicarboxylic acid 4-benzyl ester 2-*tert*-butyl ester (122) (35.2 mg, 0.051 mmol) and 10% palladium on charcoal (20 mg) whilst stirring. The nitrogen was replaced by hydrogen then
10 stirring continued for 1 hour. The hydrogen was replaced by nitrogen then the mixture filtered through celite. The filter cake was washed with ethanol (20 ml) then the filtrate concentrated *in vacuo*. The residue (28.3 mg, 100%) was used without further purification. Analytical HPLC R_t = 17.437 min; HPLC-MS 462.3 [M + 2H - Boc]⁺, 562.4 [M + H]⁺ for (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-
15 butoxycarbonylamino benzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydro pyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (123).

Preparation of (3aR, 6S, 6aS)-4-benzoyl-1-[(2S)-2-(4-*tert*-butoxycarbonyl aminobenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (124)

20

Benzoic anhydride (5.3 mg, 0.024 mmol), dimethylformamide (0.275 ml) then 4-methylmorpholine (5.2 μ l, 0.047 mmol) were added consecutively to (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-butoxycarbonylamino benzoylamino)-4-methylpentanoyl]-
25 6-hydroxy hexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (123) (12.6 mg, 0.0225 mmol, prepared as above). The solution was stirred for 90 minutes then the majority of solvents were removed *in vacuo*. The residue was dissolved in ethyl acetate (10 ml), then washed with saturated aqueous sodium hydrogen carbonate solution (5 ml), pH 3 hydrochloric acid (5 ml) and brine (5
30 ml), dried (Na₂SO₄), and the solvents removed *in vacuo*. The solid white residue (15.4 mg, 100%) was used without further purification. Data for (3aR, 6S, 6aS)-4-benzoyl-1-[(2S)-2-(4-*tert*-butoxycarbonylamino benzoylamino)-4-methyl

-451-

pentanoyl]-6-hydroxyhexahydro pyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (124): TLC (R_f = 0.25, EtOAc : heptane 2 : 1), analytical HPLC R_t = 20.787 min; HPLC-MS 333.3, 566.4 $[M + 2H - Boc]^+$, 666.4 $[M + H]^+$.

5 **Preparation of (3a*R*, 6a*S*)-4-benzoyl-1-[(2*S*)-2-(4-*tert*-butoxycarbonylamino benzoylamino)-4-methylpentanoyl]-6-oxo-hexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (126)**

10 A solution of Dess-Martin periodinane (48 mg, 0.113 mmol) in dichloromethane (1.1 ml) was added to (3a*R*, 6*S*, 6a*S*)-4-benzoyl-1-[(2*S*)-2-(4-*tert*-butoxycarbonyl aminobenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (124) (15.4 mg, 0.0225 mmol, prepared as above) under an atmosphere of nitrogen. The mixture was stirred for 3 hours then purified by flash chromatography over silica eluting with ethyl acetate :
15 heptane mixtures 1 : 4 to 1 : 1 to give (3a*R*, 6a*S*)-4-benzoyl-1-[(2*S*)-2-(4-*tert*-butoxycarbonylaminobenzoylamino)-4-methylpentanoyl]-6-oxo-hexahydro pyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (126) as an off-white solid (9.7 mg, 65%). TLC (R_f = 0.28, EtOAc : heptane 2 : 1), analytical HPLC broad peak R_t = 20.05-22.80 min; HPLC-MS single broad main UV peak 333.2,
20 664.4 $[M + H]^+$, 682.4 $[M + H_2O + H]^+$.

25 **Preparation of (3a*R*, 6a*S*)-4-amino-*N*-[(1*S*)-1-(4-benzoyl-6-oxo-hexahydro pyrrolo[3,2-*c*]pyrazole-1-carbonyl)-3-methylbutyl]benzamide (EXAMPLE 249b)**

25 Trifluoroacetic acid (0.05 ml) was added to (3a*R*, 6a*S*)-4-benzoyl-1-[(2*S*)-2-(4-*tert*-butoxycarbonylaminobenzoylamino)-4-methylpentanoyl]-6-oxo-hexahydro pyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (126) (6.4 mg, 9.7 μ mol) under an atmosphere of nitrogen. The solution was stirred for 2.5 hours then
30 diluted with dichloromethane (1 ml) and cautiously added to saturated aqueous sodium hydrogen carbonate solution (1 ml). The dichloromethane was separated then washed with water (1 ml). The saturated aqueous sodium hydrogen carbonate

-452-

solution was extracted with dichloromethane (0.5 ml) which was then washed with the water layer. The combined organic layers were dried (Na_2SO_4), and the solvents removed *in vacuo* to obtain (3aR, 6aS)-4-amino-N-[1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-c]pyrazole-1-carbonyl)-3-methylbutyl]benzamide

5 (EXAMPLE 249b) as a red solid (0.72 mg, 16%). Analytical HPLC broad peak R_t = 11.0-12.1 min; HPLC-MS broad UV peak 464.2 $[\text{M} + \text{H}]^+$, 482.4 $[\text{M} + \text{H}_2\text{O} + \text{H}]^+$, 949.3 $[\text{2M} + \text{Na}]^+$, 967.4 $[\text{2M} + \text{H}_2\text{O} + \text{Na}]^+$, 985.3 $[\text{2M} + 2\text{H}_2\text{O} + \text{Na}]^+$.

10 **Preparation of (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-butoxycarbonyl aminobenzoyl amino)-4-methylpentanoyl]-6-hydroxy-4-(3-methanesulfonyl benzoyl)hexahydropyrrolo[3,2-c]pyrazole-2-carboxylic acid *tert*-butyl ester (125)**

4-Methylmorpholine (5.7 μl , 0.052 mmol) was added to a solution of HBTU (9.9 mg, 0.026 mmol), 1-hydroxybenzotriazole monohydrate (4.0 mg, 0.026 mmol) and 3-(methylsulfonyl)benzoic acid (5.2 mg, 0.026 mmol) in dimethylformamide 15 (0.3 ml). The solution was stood for 5 minutes then added to (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-butoxycarbonylaminobenzoylamino)-4-methylpentanoyl]-6-hydroxyhexahydro pyrrolo[3,2-c]pyrazole-2-carboxylic acid *tert*-butyl ester (123) (14.7 mg, 0.026 mmol, prepared as above). The mixture was stirred for 2.5 hour then the solvents were removed *in vacuo* (water bath temperature < 37 °C). The residue was dissolved in dichloromethane (10 ml) then washed with pH 3 hydrochloric acid (5 ml), saturated aqueous sodium hydrogen carbonate solution (5 ml) and brine (5 ml), dried (Na_2SO_4), and the solvents removed *in vacuo*. The pale yellow solid residue (19.7 mg, 100%) was used without further purification. 20
Data for (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-butoxycarbonylaminobenzoylamino)-4-methylpentanoyl]-6-hydroxy-4-(3-methanesulfonylbenzoyl)hexahydropyrrolo [3,2-c]pyrazole-2-carboxylic acid *tert*-butyl ester (125): TLC (R_f = 0.05, EtOAc : heptane 2 : 1), analytical HPLC R_t = 19.945 min; HPLC-MS 333.3, 644.3 $[\text{M} + 2\text{H} - \text{Boc}]^+$, 688.3 $[\text{M} + 2\text{H} - \text{Bu}]^+$, 744.3 $[\text{M} + \text{H}]^+$, 766.3 $[\text{M} + \text{Na}]^+$.

30

-453-

Preparation of (3aR, 6aS)-1-[(2S)-2-(4-*tert*-butoxycarbonylamino)benzoyl amino)-4-methylpentanoyl]-4-(3-methanesulfonylbenzoyl)-6-oxohexahydro pyrrolo[3,2-*c*] pyrazole-2-carboxylic acid *tert*-butyl ester (127)

5 A solution of Dess-Martin periodinane (56 mg, 0.132 mmol) in dichloromethane (1.25 ml) was added to (3aR, 6S, 6aS)-1-[(2S)-2-(4-*tert*-butoxycarbonylamino benzoylamino)-4-methylpentanoyl]-6-hydroxy-4-(3-methanesulfonylbenzoyl) hexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (125) (19.7 mg, 0.0262 mmol, prepared as above) under an atmosphere of nitrogen. The
10 mixture was stirred for 4 hours then purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 3 : 7 to 4 : 1 to give (3aR, 6aS)-1-[(2S)-2-(4-*tert*-butoxycarbonylamino)benzoylamino)-4-methylpentanoyl]-4-(3-methanesulfonylbenzoyl)-6-oxohexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (127) as an off-white solid (11.1 mg, 57%). TLC (R_f = 0.10, EtOAc : heptane 2 : 1), analytical HPLC broad peak R_t = 19.20-21.70 min; HPLC-MS single broad main UV peak 333.2, 642.3 $[M + 2H - Boc]^+$, 660.3 $[M + 2H + H_2O - Boc]^+$, 686.3 $[M + 2H - Bu]^+$, 704.2 $[M + 2H + H_2O - Bu]^+$, 742.3 $[M + H]^+$, 760.3 $[M + H_2O + H]^+$.

20 **Preparation of (3aR, 6aS)-4-amino-*N*-{(1S)-1-[4-(3-methanesulfonylbenzoyl)-6-oxo-hexahydropyrrolo[3,2-*c*]pyrazole-1-carbonyl]-3-methylbutyl} benzamide (EXAMPLE 249c)**

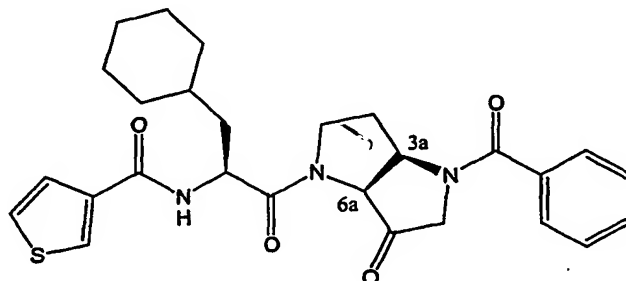
25 Trifluoroacetic acid (0.05 ml) was added to (3aR, 6aS)-1-[(2S)-2-(4-*tert*-butoxycarbonylamino)benzoylamino)-4-methylpentanoyl]-4-(3-methanesulfonyl benzoyl)-6-oxohexahydropyrrolo[3,2-*c*]pyrazole-2-carboxylic acid *tert*-butyl ester (127) (4.93 mg, 6.7 μ mol) under an atmosphere of nitrogen. The solution was stirred for 2.5 hours then diluted with dichloromethane (1 ml) and cautiously added to saturated aqueous sodium hydrogen carbonate solution (1 ml). The
30 dichloromethane was separated then washed with water (1 ml). The saturated aqueous sodium hydrogen carbonate solution was extracted with dichloromethane (0.5 ml) which was then washed with the water layer. The combined organic

-454-

layers were dried (Na_2SO_4), and the solvents removed *in vacuo* to obtain (3aR, 6aS)-4-amino-N-{(1S)-1-[4-(3-methanesulfonylbenzoyl)-6-oxo-hexahydropyrrolo [3,2-c]pyrazole-1-carbonyl]-3-methylbutyl}benzamide (EXAMPLE 249c) as a red solid (0.66 mg, 18%). Analytical HPLC broad peak $R_t = 10.2-11.4$ min; HPLC-MS broad UV peak 233.1, 542.2 $[\text{M} + \text{H}]^+$, 560.2 $[\text{M} + \text{H}_2\text{O} + \text{H}]^+$.

EXAMPLES 250 to 295 were prepared as detailed for EXAMPLES 1 and 119, substituting the appropriate carboxylic acids as required and are inhibitors of cathepsin S with K_i ranging from 10-5000nM;

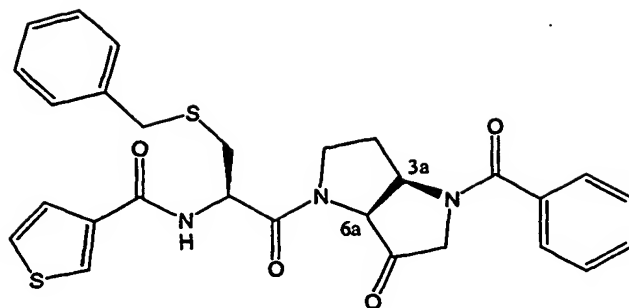
EXAMPLE 250. (3aR, 6aS)-Thiophene-3-carboxylic acid [(1S)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-1-cyclohexylmethyl-2-oxo-ethyl]-amide



HPLC $R_t = 16.4-17.2$ mins ($> 90\%$), HPLC-MS 494.2 $[\text{M} + \text{H}]^+$, 1009.4 $[2\text{M} + \text{Na}]^+$.

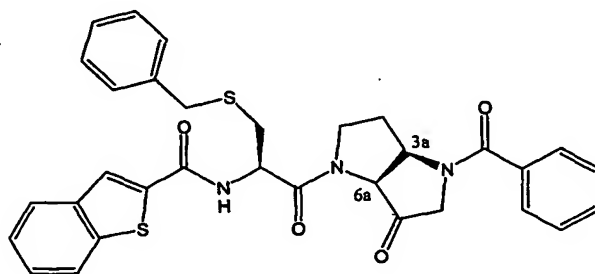
EXAMPLE 251. (3aR, 6aS)-Thiophene-3-carboxylic acid [(1R)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-amide

-455-



HPLC R_t = 14.78 mins (> 90%), HPLC-MS 534.1 $[M + H]^+$.

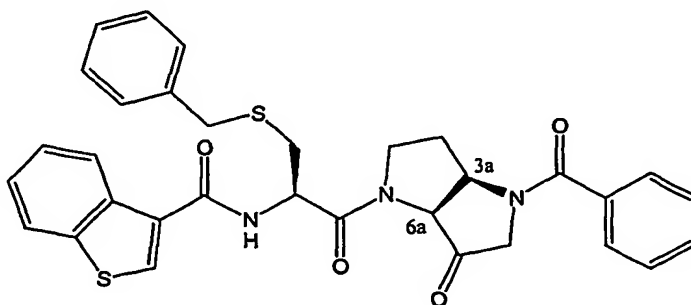
- 5 EXAMPLE 252. (3a*R*, 6a*S*)-Benzo[*b*]thiophene-2-carboxylic acid [(1*R*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-amide



10

HPLC R_t = 18.5-19.8 mins (> 85%), HPLC-MS 584.1 $[M + H]^+$.

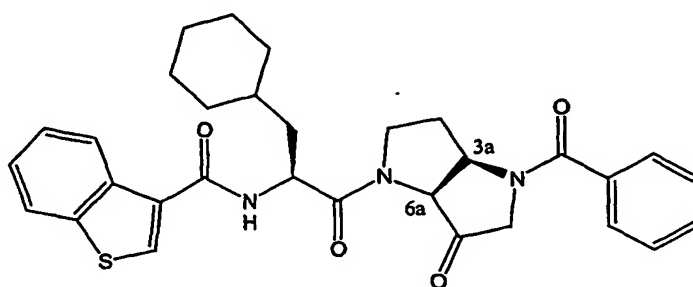
- 15 EXAMPLE 253. (3a*R*, 6a*S*)-Benzo[*b*]thiophene-3-carboxylic acid [(1*R*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-amide



-456-

HPLC Rt = 17.8-19.0 mins (> 80%), HPLC-MS 584.2 [M + H]⁺.

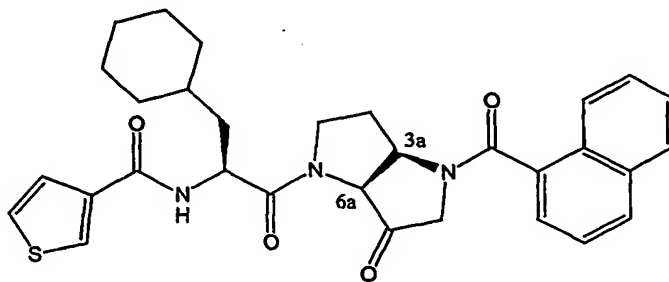
5 EXAMPLE 254. (3a*R*, 6a*S*)-Benzo[*b*]thiophene-3-carboxylic acid [(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-cyclohexylmethyl-2-oxo-ethyl]-amide



10 HPLC Rt = 19.5-20.5 mins (> 75%), HPLC-MS 544.1 [M + H]⁺.

EXAMPLE 255. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*S*)-1-cyclohexylmethyl-2-[4-(naphthalene-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-amide

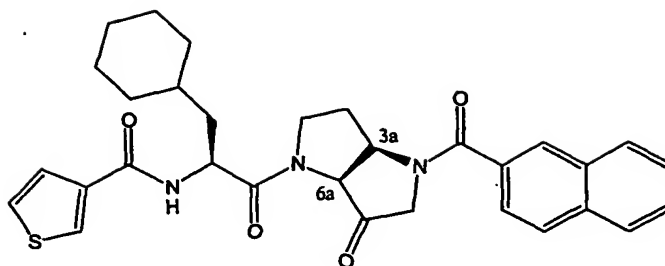
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HPLC Rt = 18.3-19.5 mins (> 80%), HPLC-MS 544.1 [M + H]⁺.

20 EXAMPLE 256. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*S*)-1-cyclohexylmethyl-2-[4-(naphthalene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-amide

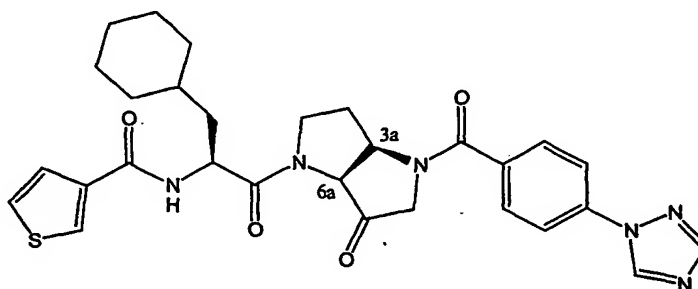
-457-



HPLC Rt = 18.9-19.7 mins (> 85%), HPLC-MS 544.1 [M + H]⁺.

5

EXAMPLE 257. (3aR, 6aS)-Thiophene-3-carboxylic acid {(1S)-1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(4-[1,2,4]triazol-1-yl-benzoyl)-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-ethyl}-amide

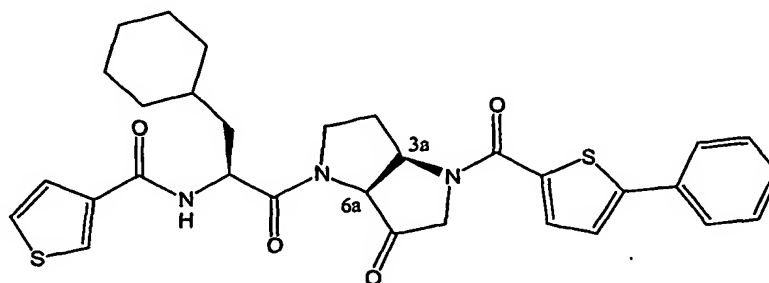


10

HPLC Rt = 15.5-16.5 mins (> 85%), HPLC-MS 561.2 [M + H]⁺.

EXAMPLE 258. (3aR, 6aS)-Thiophene-3-carboxylic acid {(1S)-1-cyclohexylmethyl-2-oxo-2-[6-oxo-4-(5-phenyl-thiophene-2-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-ethyl}-amide

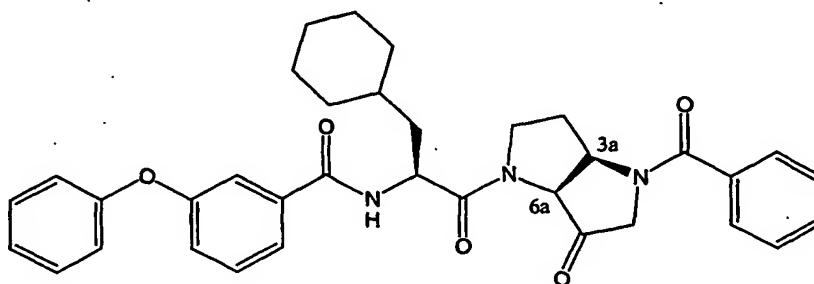
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-458-

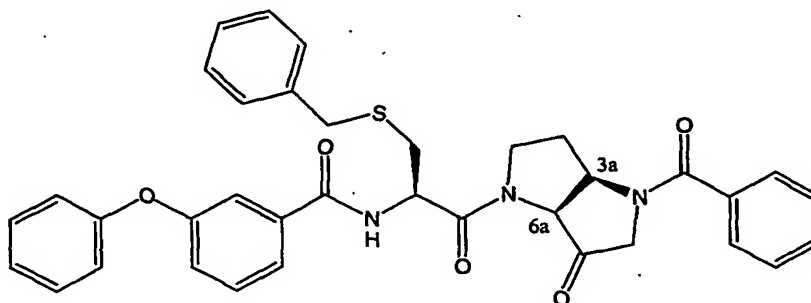
HPLC Rt = 19.5-20.2 mins (> 85%), HPLC-MS 576.1 [M + H]⁺.

EXAMPLE 259. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-
5 b] pyrrol-1-yl)-1-cyclohexylmethyl-2-oxo-ethyl]-3-phenoxy-benzamide



HPLC Rt = 19.4-20.3 mins (> 85%), HPLC-MS 580.2 [M + H]⁺.
10

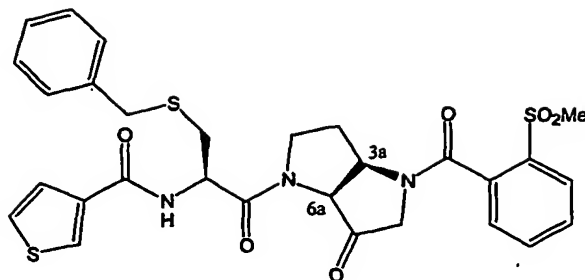
EXAMPLE 260. (3a*R*, 6a*S*)-*N*-[(1*R*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-
b] pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-3-phenoxy-benzamide



HPLC Rt = 18.3-19.6 mins (> 90%), HPLC-MS 620.2 [M + H]⁺.
15

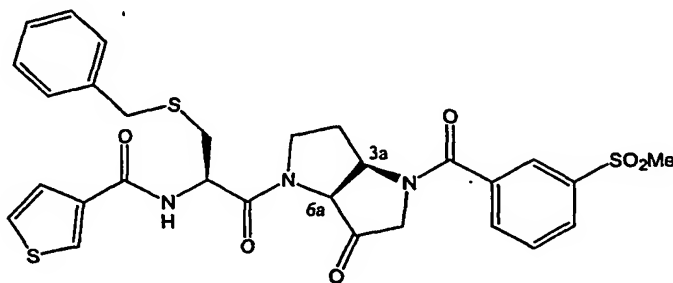
EXAMPLE 261. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*R*)-1-benzylsulfanyl
methyl-2-[4-(2-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-
20 b]pyrrol-1-yl]-2-oxo-ethyl}-amide

-459-



HPLC Rt = 14.5-15.2 mins (> 80%), HPLC-MS 612.0 [M + H]⁺.

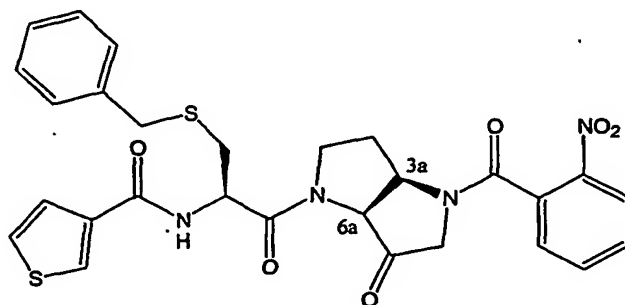
- 5 EXAMPLE 262. (3aR, 6aS)-Thiophene-3-carboxylic acid {(1R)-1-benzylsulfanyl methyl-2-[4-(3-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl}-amide



10

HPLC Rt = 14.09 mins (> 90%), HPLC-MS 612.1 [M + H]⁺.

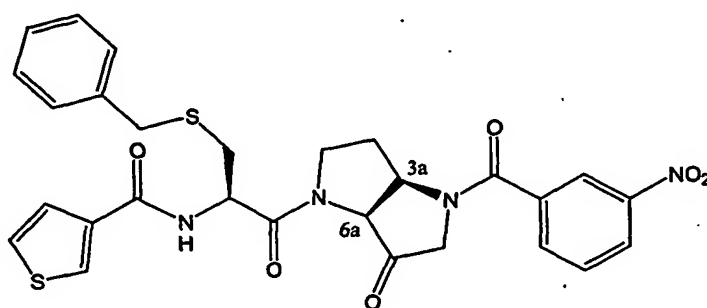
- 15 EXAMPLE 263. (3aR, 6aS)-Thiophene-3-carboxylic acid {(1R)-1-benzylsulfanyl methyl-2-[4-(2-nitro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl}-amide



-460-

HPLC Rt = 14.93 mins (> 90%), HPLC-MS 579.0 [M + H]⁺.

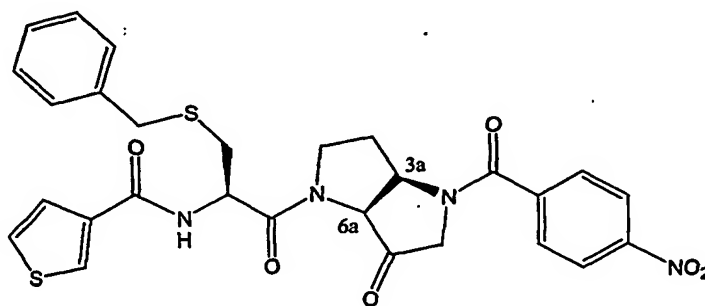
5 EXAMPLE 264. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*R*)-1-benzylsulfanyl methyl-2-[4-(3-nitro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-amide



10 HPLC Rt = 15.53 mins (> 85%), HPLC-MS 579.0 [M + H]⁺.

EXAMPLE 265. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*R*)-1-benzylsulfanyl methyl-2-[4-(4-nitro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-amide

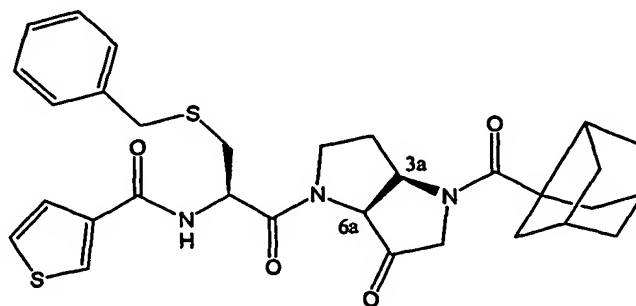
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HPLC Rt = 15.41 mins (> 90%), HPLC-MS 579.1 [M + H]⁺.

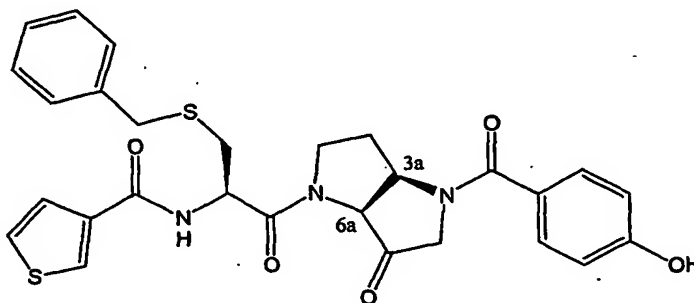
-461-

EXAMPLE 266. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*R*)-1-benzylsulfanyl methyl-2-[4-(hexahydro-2,5-methano-pentalene-3a-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-amide



HPLC Rt = 17.0-18.2 mins (> 80%), HPLC-MS 578.1 [M + H]⁺.

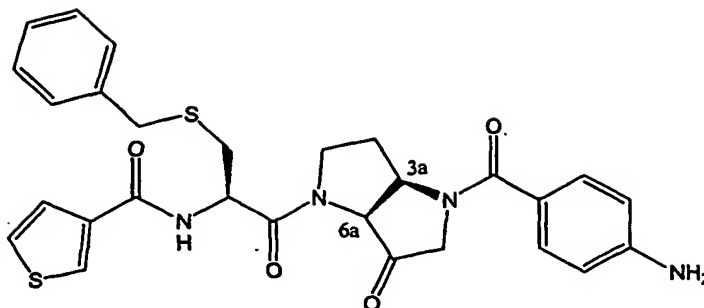
EXAMPLE 267. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*R*)-1-benzylsulfanyl methyl-2-[4-(4-hydroxy-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-amide



HPLC Rt = 13.43 mins (> 80%), HPLC-MS 550.0 [M + H]⁺.

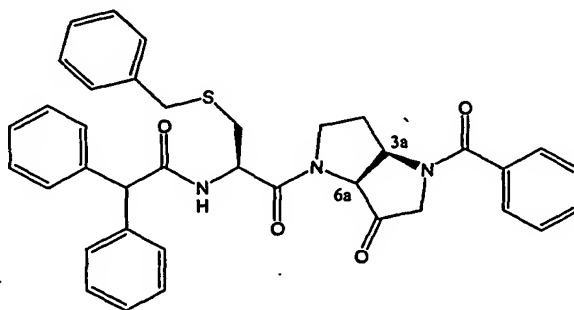
EXAMPLE 268. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*R*)-2-[4-(4-amino-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-benzylsulfanylmethyl-2-oxo-ethyl}-amide

-462-



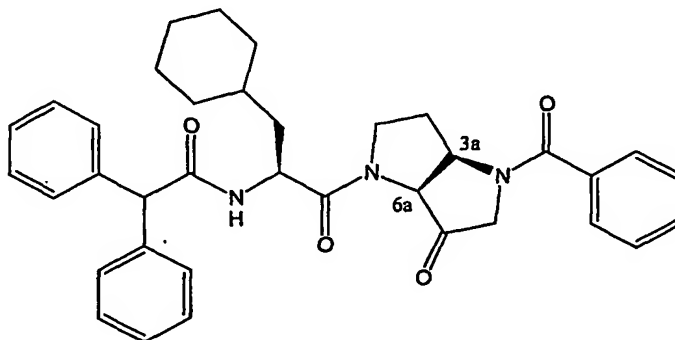
HPLC Rt = 11.8-12.4 mins (> 75%), HPLC-MS 549.1 [M + H]⁺.

- 5 EXAMPLE 269. (3a*R*, 6a*S*)-*N*-[(1*R*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-2,2-diphenyl-acetamide



- 10 HPLC Rt = 19.1-20.3 mins (> 90%), HPLC-MS 618.2 [M + H]⁺.

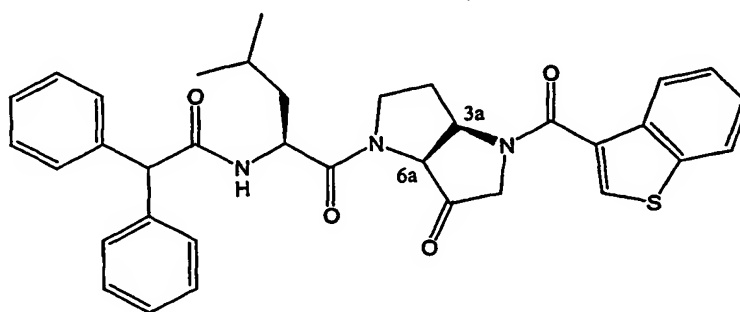
EXAMPLE 270. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-cyclohexylmethyl-2-oxo-ethyl]-2,2-diphenyl-acetamide



-463-

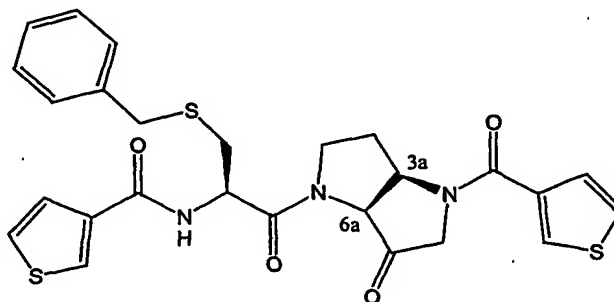
HPLC Rt = 19.9-21.0 mins (> 90%), HPLC-MS 578.3 [M + H]⁺.

EXAMPLE 271. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-[4-(Benzo[*b*]thiophene-3-carbonyl)-6-oxo-
5 hexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl]-3-methyl-butyl}-2,2-diphenyl-
acetamide



10 HPLC Rt = 19.4-20.7 mins (> 90%), HPLC-MS 594.2 [M + H]⁺.

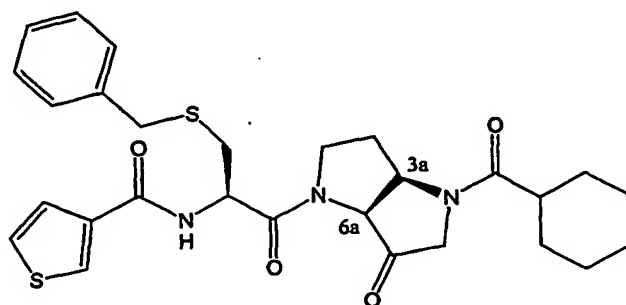
EXAMPLE 272. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*R*)-1-benzylsulfanyl
methyl-2-oxo-2-[6-oxo-4-(thiophene-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-
15 1-yl]-ethyl}-amide



HPLC Rt = 14.56 mins (> 90%), HPLC-MS 540.0 [M + H]⁺.

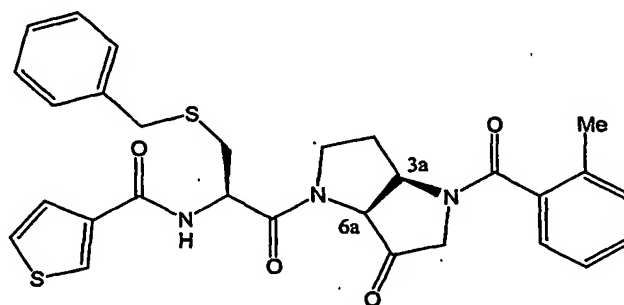
-464-

EXAMPLE 273. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid [(1*R*)-1-benzylsulfanyl methyl-2-(4-cyclohexanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-2-oxo-ethyl]-amide



HPLC R_t = 15.5-16.4 mins (> 75%), HPLC-MS 540.1 $[M + H]^+$.

EXAMPLE 274. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*R*)-1-benzylsulfanyl methyl-2-[4-(2-methyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-amide

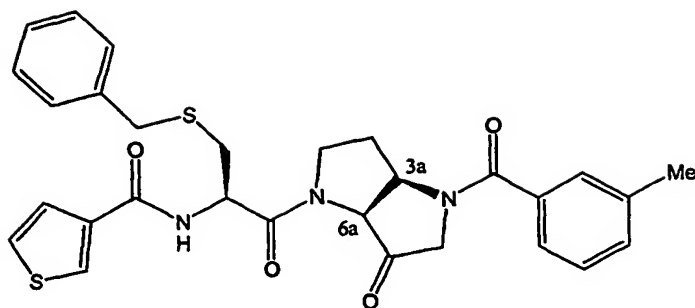


HPLC R_t = 16.0-17.9 mins (> 90%), HPLC-MS 548.1 $[M + H]^+$.

EXAMPLE 275. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*R*)-1-benzylsulfanyl methyl-2-[4-(3-methyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-amide

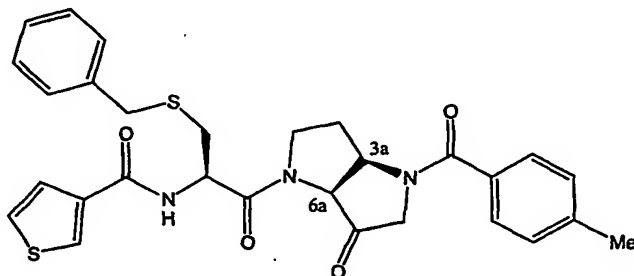
20

-465-



HPLC Rt = 16.3-17.8 mins (> 90%), HPLC-MS 548.1 [M + H]⁺.

- 5 EXAMPLE 276. (3aR, 6aS)-Thiophene-3-carboxylic acid {(1R)-1-benzylsulfanylmethyl-2-oxo-ethyl-2-oxo-pyrrolo[3,2-b]pyrrol-1-yl)-4-(4-methylbenzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl-2-oxo-ethyl}-amide

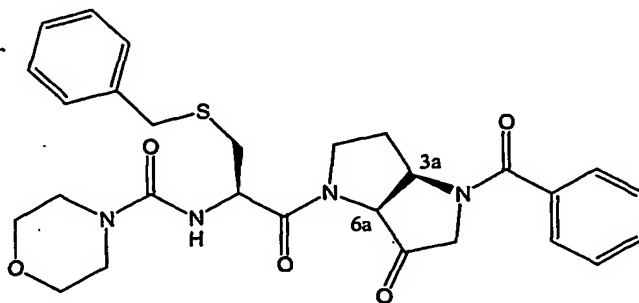


10

HPLC Rt = 15.5-16.8 mins (> 90%), HPLC-MS 548.1 [M + H]⁺.

- EXAMPLE 277. (3aR, 6aS)-Morpholine-4-carboxylic acid [(1R)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-amide

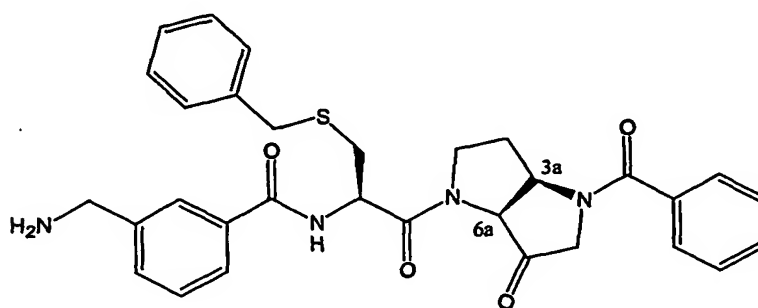
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-466-

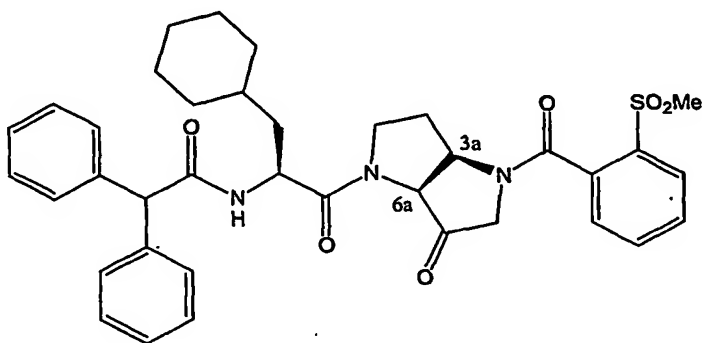
HPLC Rt = 12.5-13.8 mins (> 80%), HPLC-MS 537.1 [M + H]⁺.

EXAMPLE 278. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-[(1*R*)-2-(4-benzoyl-6-oxo-
 5 hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-
 benzamide



10 HPLC Rt = 12.0-13.4 mins (> 80%), HPLC-MS 557.2 [M + H]⁺.

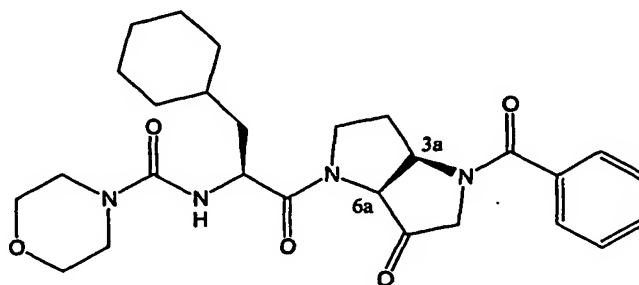
EXAMPLE 279. (3a*R*, 6a*S*)-*N*-{(1*S*)-1-Cyclohexylmethyl-2-[4-(2-
 methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-
 15 ethyl}-2,2-diphenyl-acetamide



HPLC Rt = 20.1-21.4 mins (> 90%), HPLC-MS 656.2 [M + H]⁺.

-467-

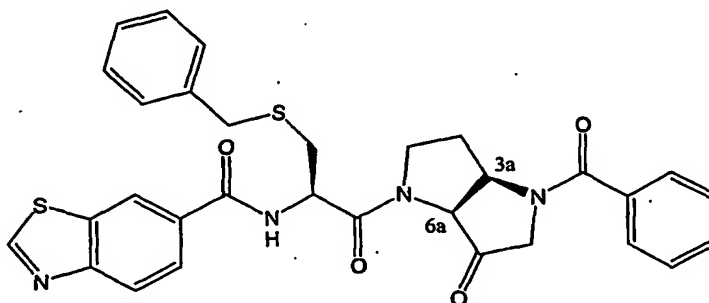
EXAMPLE 280. (3a*R*, 6a*S*)-Morpholine-4-carboxylic acid [(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-cyclohexylmethyl-2-oxo-ethyl]-amide



5

HPLC R_t = 14.96 mins (> 95%), HPLC-MS 497.2 $[M + H]^+$, 515.2 $[M + H + H_2O]^+$.

10 EXAMPLE 281. (3a*R*, 6a*S*)-Benzothiazole-6-carboxylic acid [(1*R*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-amide

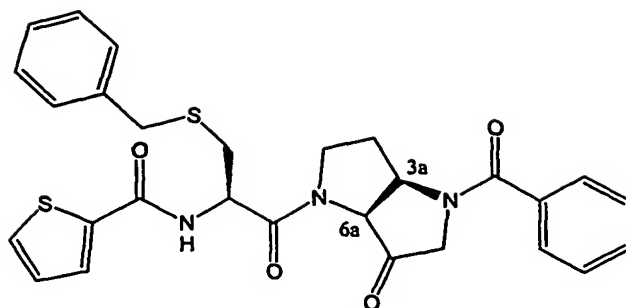


15

HPLC R_t = 15.15 mins (> 85%), HPLC-MS 585.1 $[M + H]^+$, 603.1 $[M + H + H_2O]^+$.

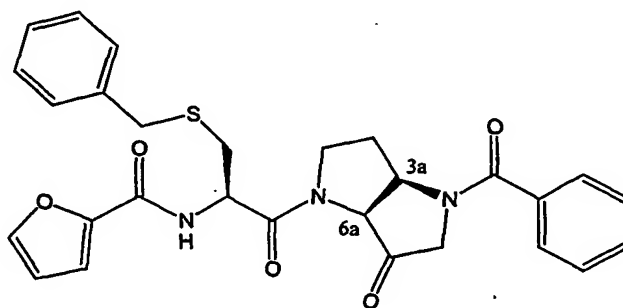
20 EXAMPLE 282. (3a*R*, 6a*S*)-Thiophene-2-carboxylic acid [(1*R*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-amide

-468-



HPLC Rt = 15.06 mins (> 85%), HPLC-MS 534.0 [M + H]⁺.

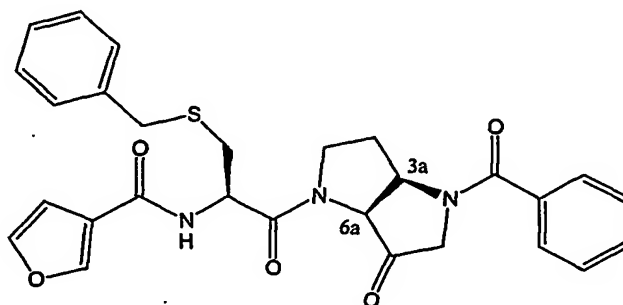
- 5 EXAMPLE 283. (3aR, 6aS)-Furan-2-carboxylic acid [(1R)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-amide



- 10 HPLC Rt = 14.1-15.4 mins (> 80%), HPLC-MS 518.1 [M + H]⁺, 536.1 [M + H + H₂O]⁺.

EXAMPLE 284. (3aR, 6aS)-Furan-3-carboxylic acid [(1R)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-amide

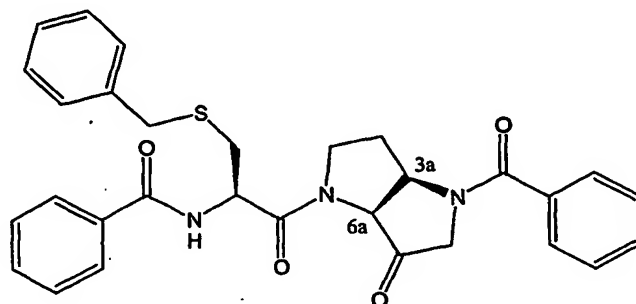
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-469-

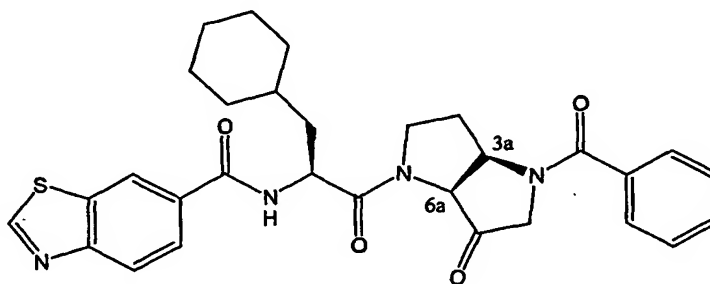
HPLC Rt = 15.7-17.3 mins (> 85%), HPLC-MS 518.1 [M + H]⁺.

EXAMPLE 285. (3a*R*, 6a*S*)-*N*-[(1*R*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-
5 b] pyrrol-1-yl)-1-benzylsulfanylmethyl-2-oxo-ethyl]-benzamide



HPLC Rt = 15.34 mins (> 90%), HPLC-MS 528.1 [M + H]⁺.

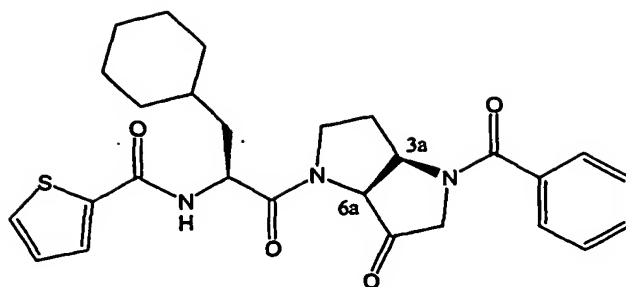
EXAMPLE 286. (3a*R*, 6a*S*)-Benzothiazole-6-carboxylic acid [(1*S*)-2-(4-benzoyl-
6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-cyclohexylmethyl-2-oxo-ethyl]-
amide



HPLC Rt = 18.25 mins (> 90%), HPLC-MS 5452 [M + H]⁺.

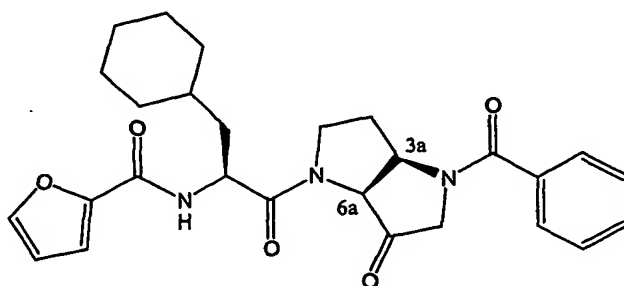
EXAMPLE 287. (3a*R*, 6a*S*)-Thiophene-2-carboxylic acid [(1*S*)-2-(4-benzoyl-6-
20 oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-cyclohexylmethyl-2-oxo-ethyl]-
amide

-470-



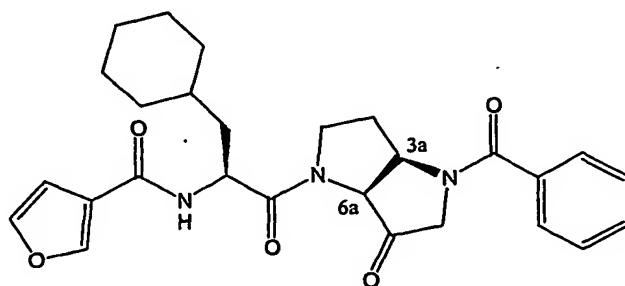
HPLC Rt = 18.28 mins (> 90%), HPLC-MS 494.1 [M + H]⁺.

- 5 **EXAMPLE 288.** (3a*R*, 6a*S*)-Furan-2-carboxylic acid [(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-cyclohexylmethyl-2-oxo-ethyl]-amide



- 10 HPLC Rt = 16.66 mins (> 90%), HPLC-MS 478.1 [M + H]⁺, 977.3 [2M + Na]⁺.

- EXAMPLE 289.** (3a*R*, 6a*S*)-Furan-3-carboxylic acid [(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-cyclohexylmethyl-2-oxo-ethyl]-amide

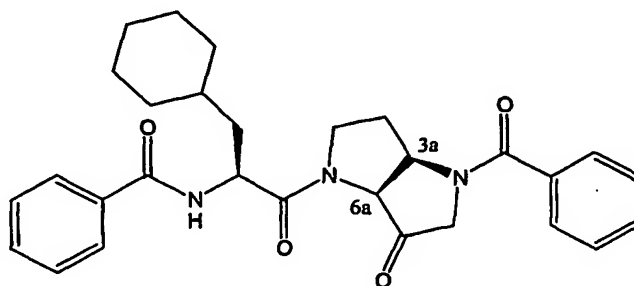


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HPLC Rt = 16.37 mins (> 90%), HPLC-MS 478.1 [M + H]⁺, 977.3 [2M + Na]⁺.

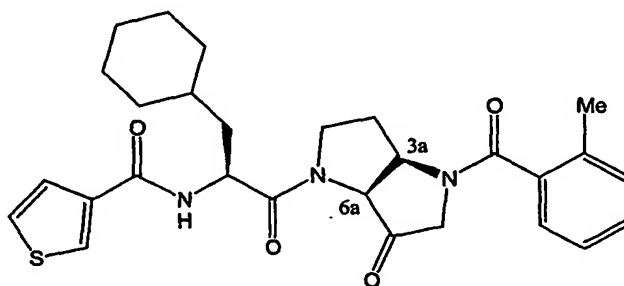
-471-

EXAMPLE 290. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl)-1-cyclohexylmethyl-2-oxo-ethyl]-benzamide



HPLC Rt = 16.71 mins (> 95%), HPLC-MS 488.2 [M + H]⁺, 997.3 [2M + Na]⁺.

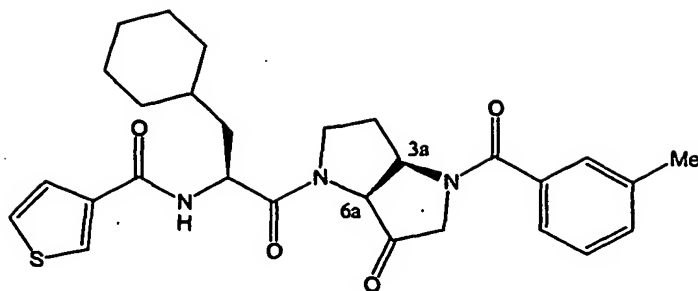
EXAMPLE 291. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*S*)-1-
cyclohexylmethyl-2-[4-(2-methyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-2-oxo-ethyl}-amide



HPLC Rt = 15.65 mins (> 95%), HPLC-MS 508.2 [M + H]⁺, 526.2 [M + H + H₂O]⁺.

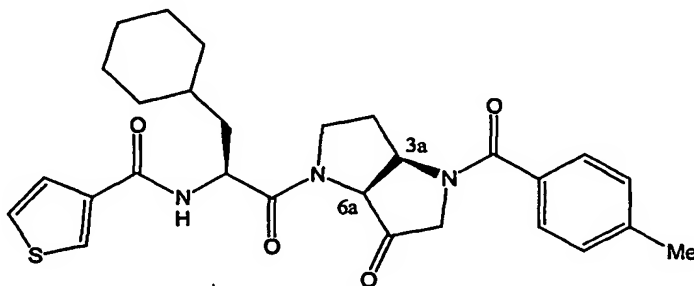
EXAMPLE 292. (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*S*)-1-
cyclohexylmethyl-2-[4-(3-methyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-
b]pyrrol-1-yl]-2-oxo-ethyl}-amide

-472-



HPLC Rt = 16.10 mins (> 90%), HPLC-MS 508.1 [M + H]⁺.

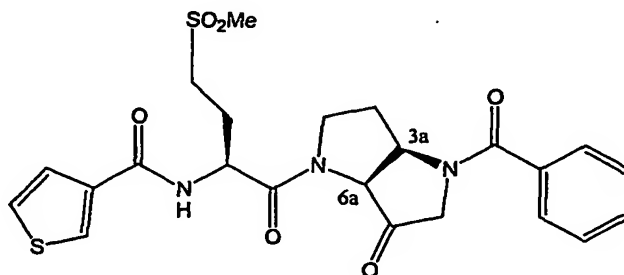
- 5 **EXAMPLE 293.** (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid {(1*S*)-1-cyclohexylmethyl-2-[4-(4-methyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-amide



10

HPLC Rt = 15.88 mins (> 90%), HPLC-MS 508.1 [M + H]⁺.

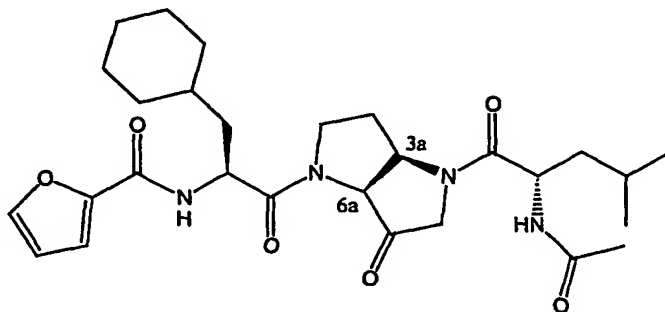
- 15 **EXAMPLE 294.** (3a*R*, 6a*S*)-Thiophene-3-carboxylic acid [(1*R*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-methanesulfonylmethyl-2-oxo-ethyl]-amide



-473-

HPLC Rt = 8.61 mins (> 90%), HPLC-MS 504.1 [M + H]⁺.

EXAMPLE 295. (3a*R*, 6a*S*)-Furan-2-carboxylic acid {(1*S*)-2-[4-((2*S*)-2-acetylamino-4-methyl-pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-cyclohexylmethyl-2-oxo-ethyl}-amide



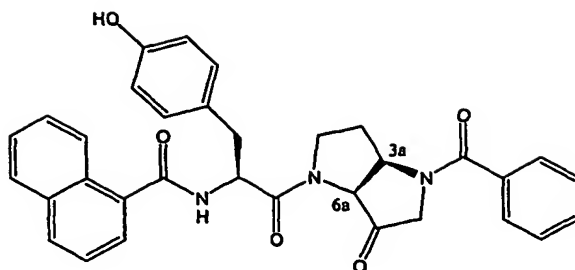
HPLC Rt = 14.35 mins (> 95%), HPLC-MS 529.2 [M + H]⁺.

In addition, EXAMPLES 7, 8, 9, 10, 12, 13, 14, 16, 17, 19, 20, 37, 39, 59, 61, 65, 85, 86, 87, 88, 89, 90, 91, 92, 93, 98, 103, 123, 145, 151, 154, 158, 159, 161, 164, 170, 171, 172, 173, 174, 185, 187, 193, 194, 245, 247, 249a, 249b, 249c, 298, 303, 310, 314, 315, 316, 317, 323, 329, 330, 334, 335 and 340 have utility as inhibitors of cathepsin S with *K_i* less than 5000nM.

EXAMPLES 296 to 345 were prepared as detailed for EXAMPLES 1 and 119, substituting the appropriate carboxylic acids as required and are inhibitors of cathepsin L with *K_i* ranging from 10-5000nM;

EXAMPLE 296. (3a*R*, 6a*S*)-Naphthalene-1-carboxylic acid [(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-(4-hydroxybenzyl)-2-oxo-ethyl]-amide

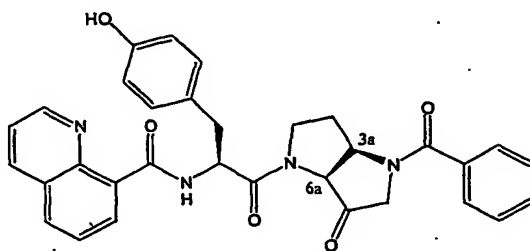
-474-



HPLC R_t = 13.5-14.4 mins (> 90%), HPLC-MS 548.2 $[M + H]^+$, 1117.4 $[2M + Na]^+$.

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EXAMPLE 297. (3aR, 6aS)-Quinoline-8-carboxylic acid [(1S)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide

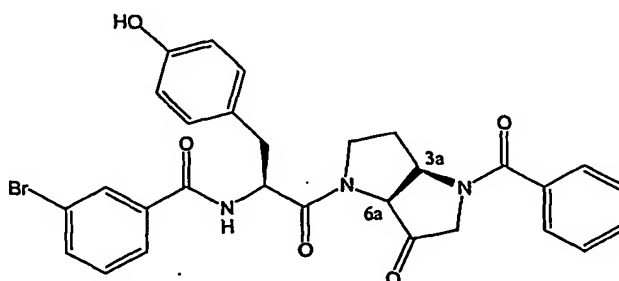


10

HPLC R_t = 11.79 mins (> 85%), HPLC-MS 549.2 $[M + H]^+$, 567.3 $[M + H + H_2O]^+$.

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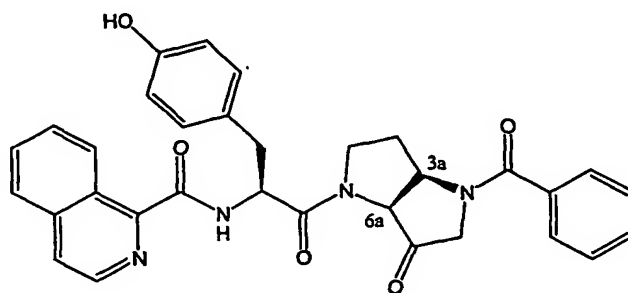
EXAMPLE 298. (3aR, 6aS)-N-[(1S)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b] pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-3-bromo-benzamide



-475-

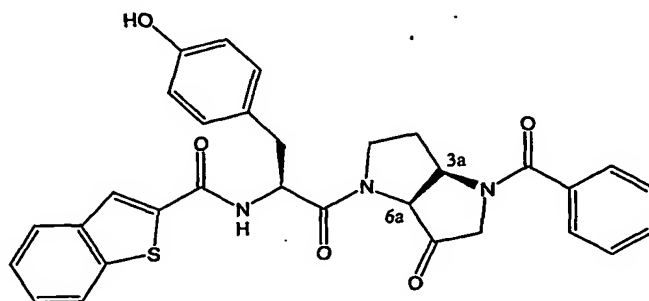
HPLC Rt = 13.21 mins (> 95%), HPLC-MS 576.1 / 578.1 [M + H]⁺.

EXAMPLE 299. (3a*R*, 6a*S*)-Isoquinoline-1-carboxylic acid [(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide



HPLC Rt = 14.1-15.1 mins (> 85%), HPLC-MS 549.2 [M + H]⁺, 567.2 [M + H + H₂O]⁺.

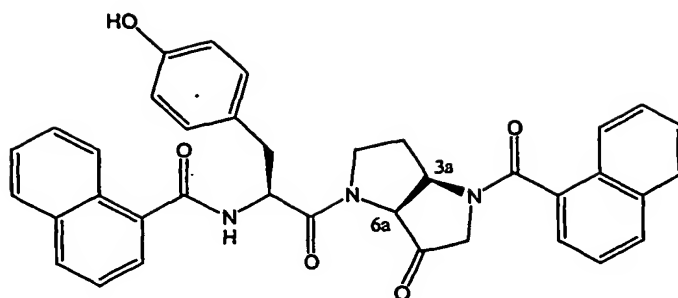
EXAMPLE 300. (3a*R*, 6a*S*)-Benzo[*b*]thiophene-2-carboxylic acid [(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide



HPLC Rt = 14.8-15.6 mins (> 85%), HPLC-MS 554.2 [M + H]⁺.

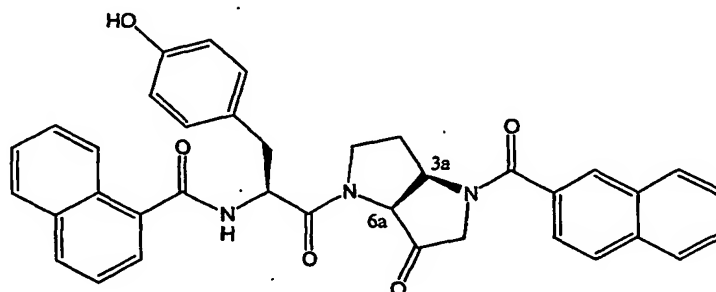
EXAMPLE 301. (3a*R*, 6a*S*)-Naphthalene-1-carboxylic acid {(1*S*)-1-(4-hydroxy-benzyl)-2-[4-(naphthalene-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-amide

-476-



HPLC Rt = 15.5-16.8 mins (> 85%), HPLC-MS 598.2 [M + H]⁺, 616.2 [M + H + H₂O]⁺.

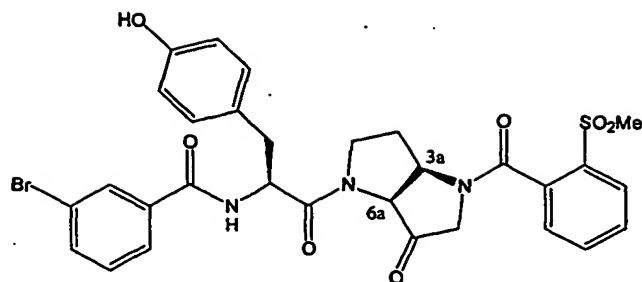
EXAMPLE 302. (3aR, 6aS)-Naphthalene-1-carboxylic acid {(1S)-1-(4-hydroxy-benzyl)-2-[4-(naphthalene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl}-amide



HPLC Rt = 16.0-16.9 mins (> 90%), HPLC-MS 598.2 [M + H]⁺.

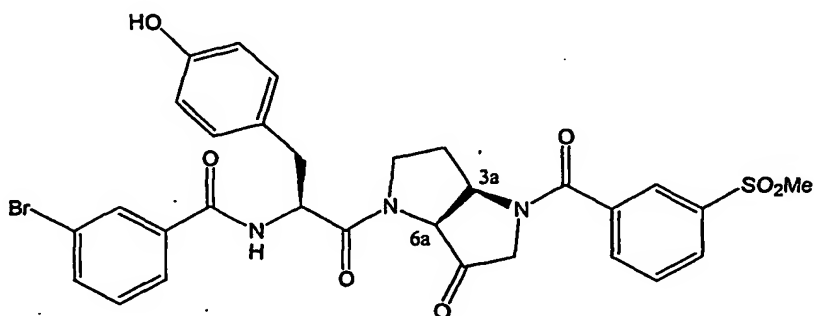
EXAMPLE 303. (3aR, 6aS)-3-Bromo-N-{(1S)-1-(4-hydroxy-benzyl)-2-[4-(2-methane sulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl}-benzamide

-477-



HPLC Rt = 12.66 mins (> 90%), HPLC-MS 654.0 / 656.0 [M + H]⁺.

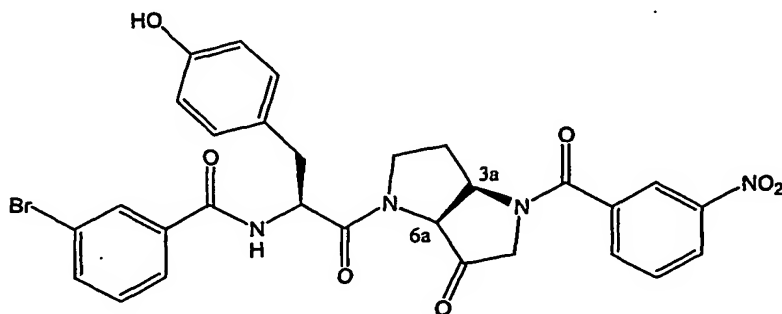
- 5 EXAMPLE 304. (3aR, 6aS)-3-Bromo-N-((1S)-1-(4-hydroxy-benzyl)-2-[4-(3-methane sulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl)-benzamide



10

HPLC Rt = 12.95 mins (> 75%), HPLC-MS 654.0 / 656.0 [M + H]⁺.

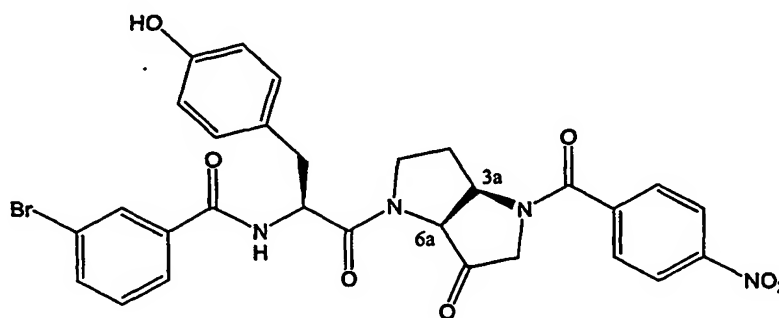
- 15 EXAMPLE 305. (3aR, 6aS)-3-Bromo-N-((1S)-1-(4-hydroxy-benzyl)-2-[4-(3-nitro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl)-benzamide



-478-

HPLC Rt = 13.52 mins (> 90%), HPLC-MS 621.0 / 623.0 [M + H]⁺.

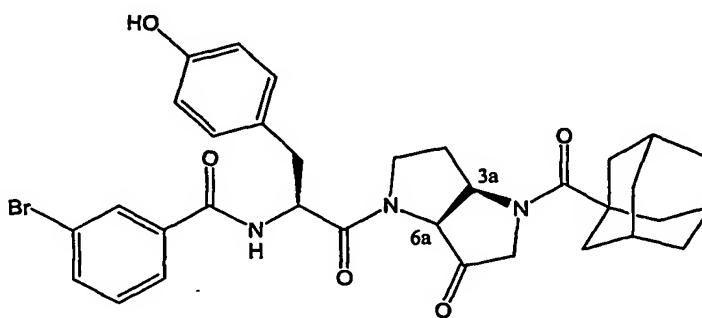
5 EXAMPLE 306. (3a*R*, 6a*S*)-3-Bromo-*N*-{[(1*S*)-1-(4-hydroxy-benzyl)-2-[4-(4-nitro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl]-2-oxo-ethyl}-benzamide



10 HPLC Rt = 13.50 mins (> 95%), HPLC-MS 621.0 / 623.0 [M + H]⁺.

EXAMPLE 307. (3a*R*, 6a*S*)-*N*-{[(1*S*)-2-[4-(Adamantane-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-3-bromo-benzamide

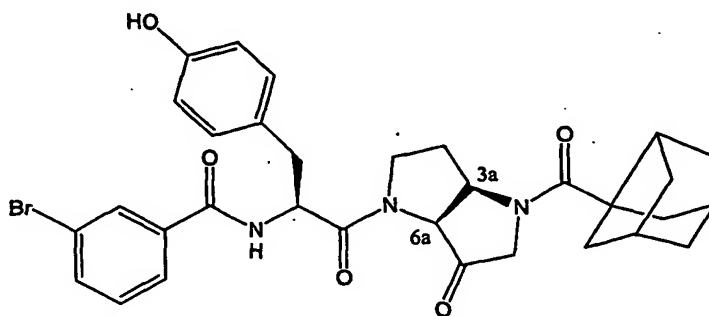
15



HPLC Rt = 15.9-17.3 mins (> 50%), HPLC-MS 634.0 / 636.0 [M + H]⁺.

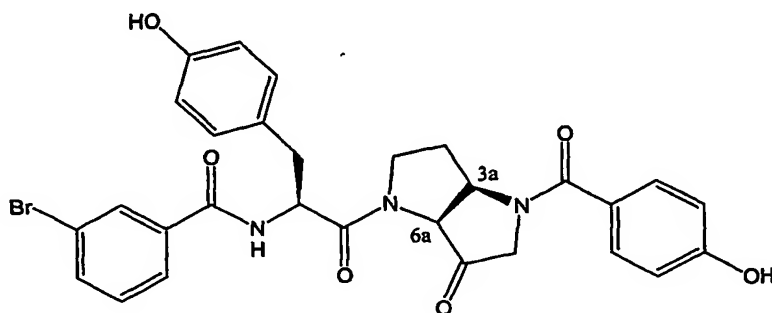
-479-

EXAMPLE 308. (3a*R*, 6a*S*)-3-Bromo-*N*-[(1*S*)-2-[4-(hexahydro-2,5-methano-pentalene-3a-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-benzamide



HPLC R_t = 14.7-16.2 mins (> 80%), HPLC-MS 620.0 / 622.0 $[M + H]^+$, 638.1 / 640.1 $[M + H + H_2O]^+$.

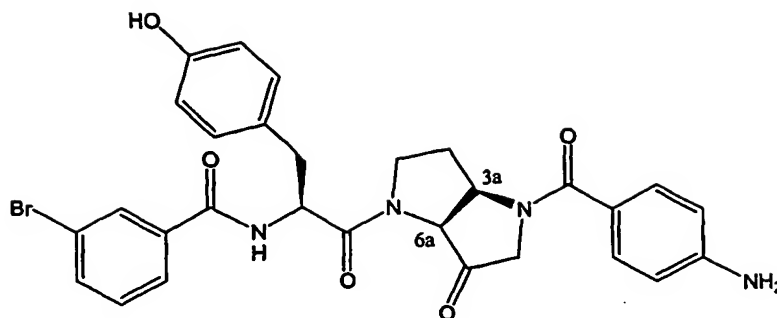
EXAMPLE 309. (3a*R*, 6a*S*)-3-Bromo-*N*-[(1*S*)-2-[4-(4-hydroxy-benzoyl)-6-oxo-hexa hydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-benzamide



HPLC R_t = 11.92 mins (> 80%), HPLC-MS 592.0 / 594.0 $[M + H]^+$.

EXAMPLE 310. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-[4-(4-Amino-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-3-bromo-benzamide

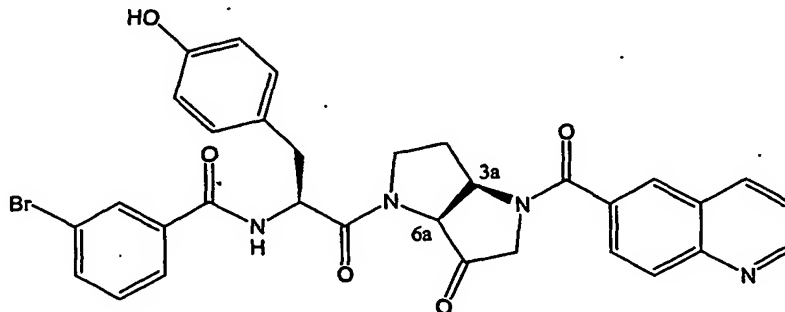
-480-



HPLC Rt = 9.9-10.6 mins (> 75%), HPLC-MS 591.0 / 593.0 $[M + H]^+$, 609.0 / 611.0 $[M + H + H_2O]^+$.

5

EXAMPLE 311. (3aR, 6aS)-3-Bromo-N-((1S)-1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(quinoline-6-carbonyl)-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-ethyl)-benzamide



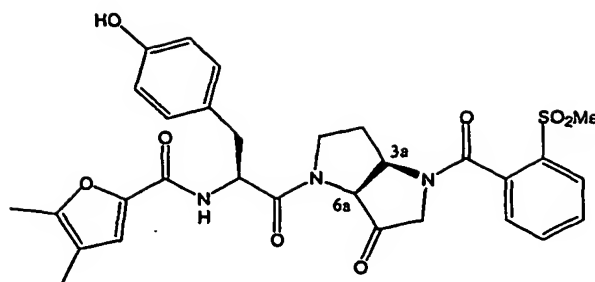
10

HPLC Rt = 11.13 mins (> 75%), HPLC-MS 627.0 / 629.0 $[M + H]^+$, 645.0 / 647.0 $[M + H + H_2O]^+$.

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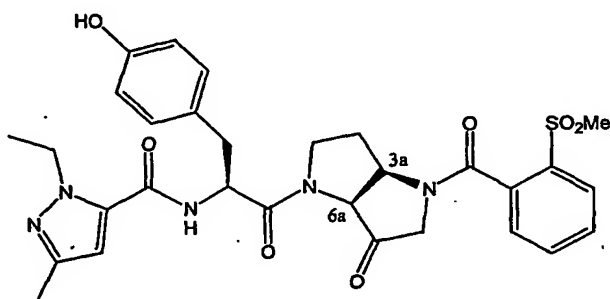
EXAMPLE 312. (3aR, 6aS)-4,5-Dimethyl-furan-2-carboxylic acid {(1S)-1-(4-hydroxy-benzyl)-2-[4-(2-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl}-amide

-481-



HPLC R_t = 11.43 mins (> 90%), HPLC-MS 594.1 $[M + H]^+$.

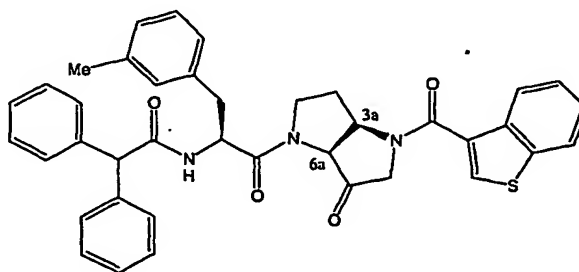
- 5 EXAMPLE 313. (3a*R*, 6a*S*)-2-Ethyl-5-methyl-2*H*-pyrazole-3-carboxylic acid
 {(1*S*)-1-(4-hydroxy-benzyl)-2-[4-(2-methanesulfonylbenzoyl)-6-oxo-
 hexahydropyrrolo[3,2-*b*] pyrrol-1-yl]-2-oxo-ethyl}-amide



10

HPLC R_t = 10.03 mins (> 90%), HPLC-MS 608.1 $[M + H]^+$, 626.1 $[M + H + H_2O]^+$.

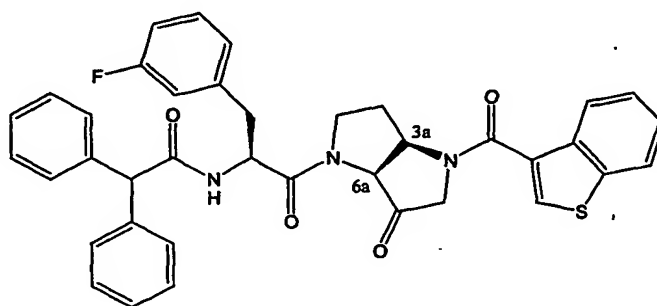
- 15 EXAMPLE 314. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-[4-(Benzo[*b*]thiophene-3-carbonyl)-6-oxo-
 hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-(3-methyl-benzyl)-2-oxo-ethyl]-2,2-
 diphenyl-acetamide



-482-

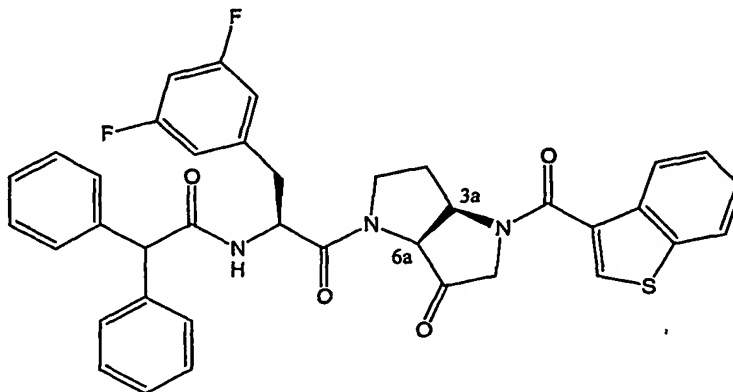
HPLC Rt = 20.2-21.4 mins (> 95%), HPLC-MS 642.2 [M + H]⁺.

EXAMPLE 315. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-[4-(Benzo[*b*]thiophene-3-carbonyl)-6-oxo-
5 hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-(3-fluoro-benzyl)-2-oxo-ethyl]-2,2-
diphenyl-acetamide



10 HPLC Rt = 19.7-21.0 mins (> 90%), HPLC-MS 646.2 [M + H]⁺.

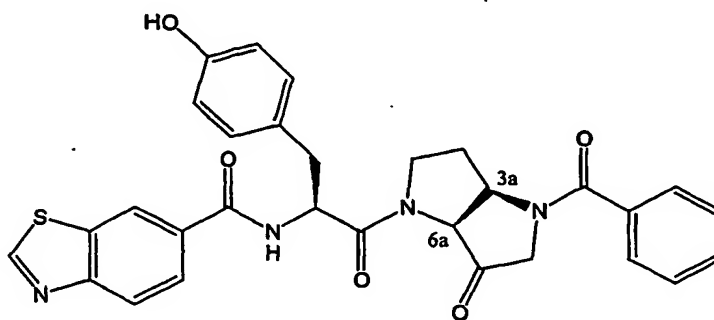
EXAMPLE 316. (3*R*, 6*aS*)-*N*-[(1*S*)-2-[4-(Benzo[*b*]thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-(3,5-difluoro-benzyl)-2-oxo-ethyl]-2,2-diphenyl-acetamide



HPLC Rt = 20.1-21.3 mins (> 90%), HPLC-MS 664.2 [M + H]⁺.

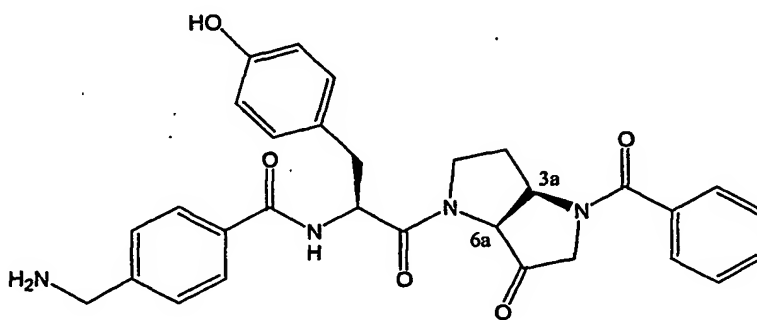
-483-

EXAMPLE 317. (3a*R*, 6a*S*)-Benzothiazole-6-carboxylic acid [(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide



HPLC Rt = 12.02 mins (> 95%), HPLC-MS 555.1 [M + H]⁺.

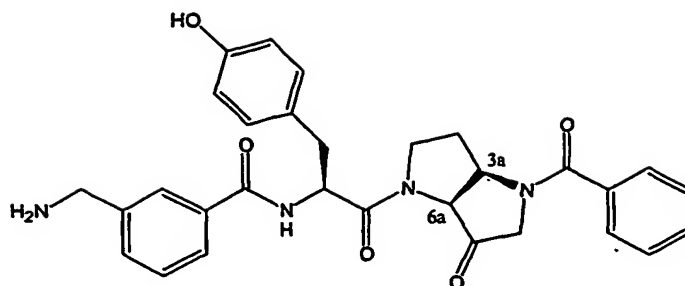
EXAMPLE 318. (3a*R*, 6a*S*)-4-Aminomethyl-*N*-[(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-benzamide



HPLC Rt = 8.92 mins (> 95%), HPLC-MS 527.2 [M + H]⁺, 545.2 [M + H + H₂O]⁺.

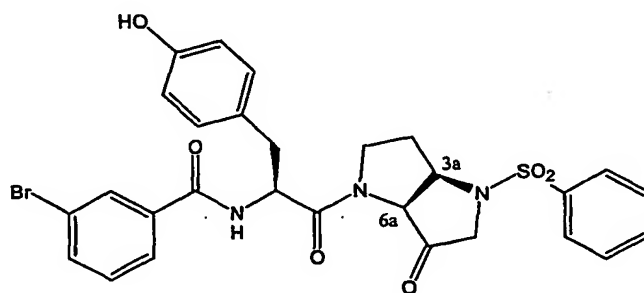
EXAMPLE 319. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-[(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-benzamide

-484-



HPLC Rt = 9.14 mins (> %), HPLC-MS 527.2 $[M + H]^+$, 545.3 $[M + H + H_2O]^+$.

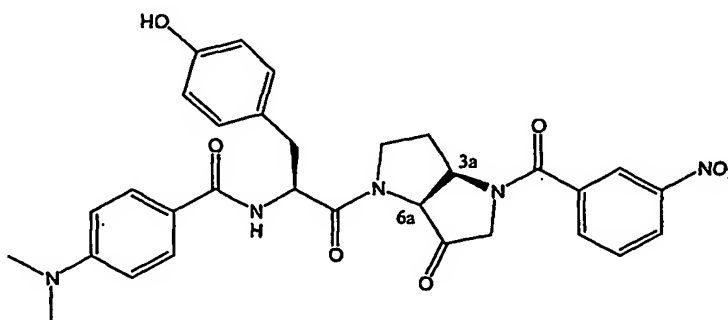
- 5 EXAMPLE 320. (3aR, 6aS)-N-[(1S)-2-(4-Benzenesulfonyl-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-3-bromo-benzamide



10

HPLC Rt = 16.1-17.9 mins (> 90%), HPLC-MS 612.0 / 614.0 $[M + H]^+$.

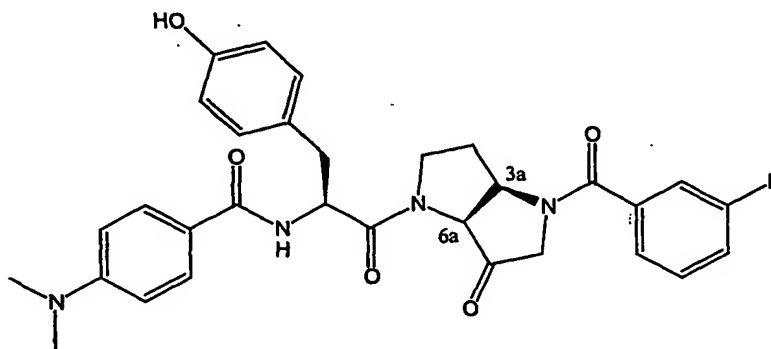
- 15 EXAMPLE 321. (3aR, 6aS)-4-Dimethylamino-N-[(1S)-1-(4-hydroxy-benzyl)-2-[4-(3-nitro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl]-benzamide



-485-

HPLC Rt = 10.75 mins (> 80%), HPLC-MS 586.2 [M + H]⁺, 604.2 [M + H + H₂O]⁺.

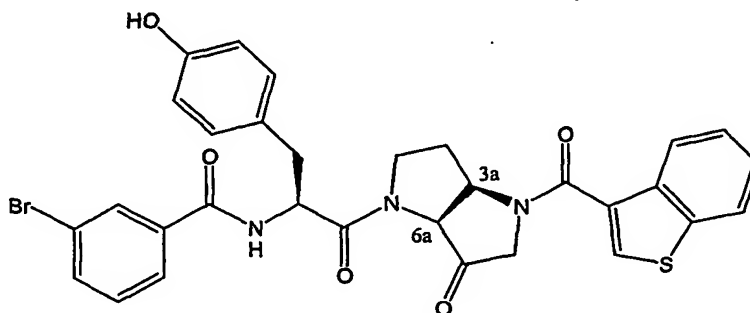
5 EXAMPLE 322. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-[(1*S*)-2-[4-(3-fluoro-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-benzamide



10

HPLC Rt = 10.59 mins (> 90%), HPLC-MS 559.2 [M + H]⁺, 577.2 [M + H + H₂O]⁺.

15 EXAMPLE 323. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-[4-(Benzo[*b*]thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-3-bromo-benzamide

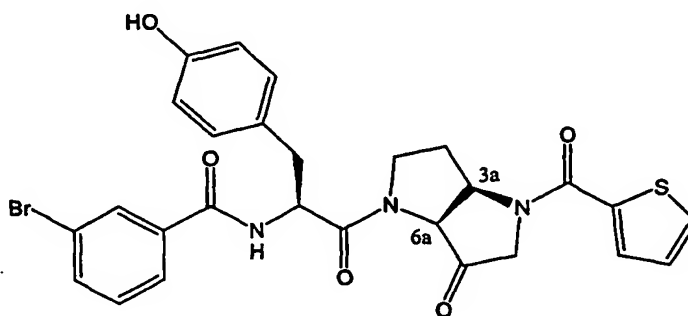


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HPLC Rt = 14.61 mins (> 90%), HPLC-MS 632.0 / 634.0 [M + H]⁺.

-486-

EXAMPLE 324. (3a*R*, 6a*S*)-3-Bromo-*N*-{(1*S*)-1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(thiophene-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide

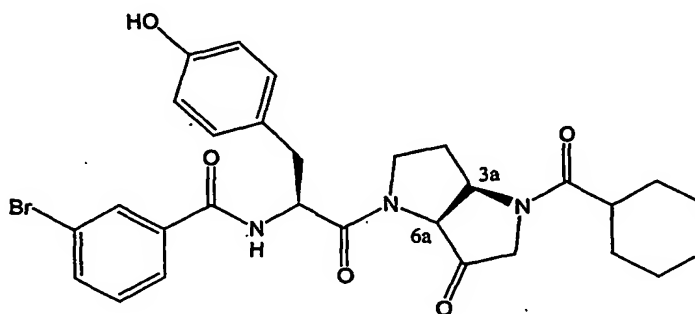


5

HPLC R_t = 12.93 mins (> 90%), HPLC-MS 582.0 / 584.0 $[M + H]^+$.

EXAMPLE 325. (3a*R*, 6a*S*)-3-Bromo-*N*-[(1*S*)-2-(4-cyclohexanecarbonyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-benzamide

10



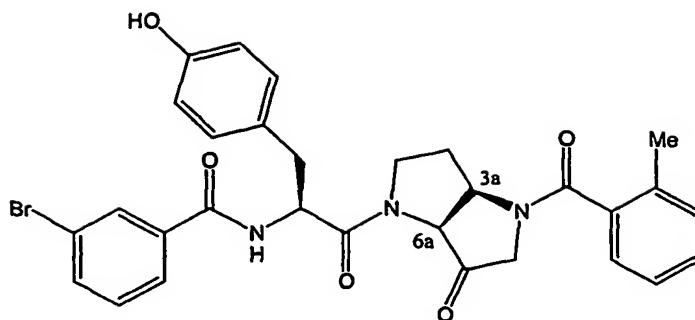
15

HPLC R_t = 15.0-17.0 mins (> 90%), HPLC-MS 582.1 / 584.1 $[M + H]^+$.

EXAMPLE 326. (3a*R*, 6a*S*)-3-Bromo-*N*-{(1*S*)-1-(4-hydroxy-benzyl)-2-[4-(2-methyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-benzamide

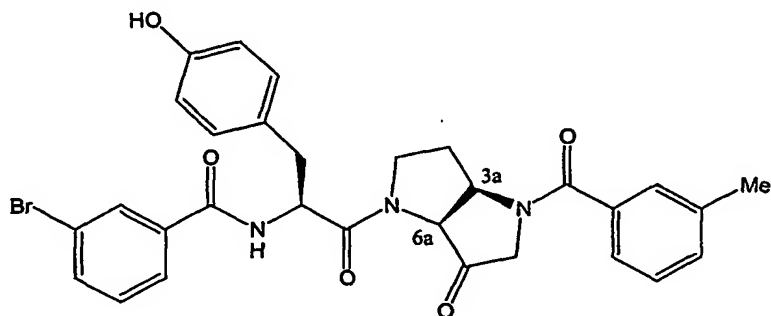
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-487-



HPLC Rt = 14.4-16.1 mins (> 90%), HPLC-MS 590.0 / 592.0 [M + H]⁺.

- 5 EXAMPLE 327. (3aR, 6aS)-3-Bromo-N-((1S)-1-(4-hydroxy-benzyl)-2-[4-(3-methyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl)-benzamide

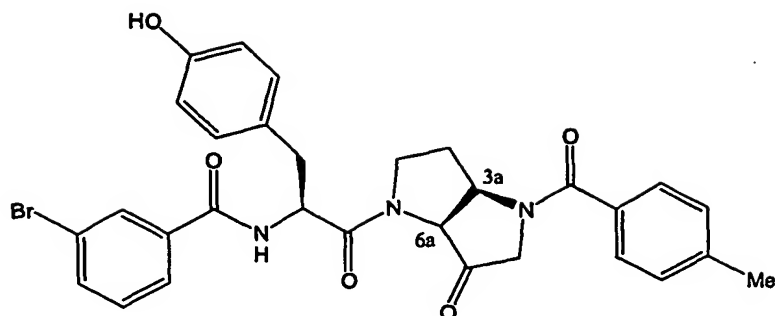


10

HPLC Rt = 14.4-15.8 mins (> 90%), HPLC-MS 590.0 / 592.0 [M + H]⁺.

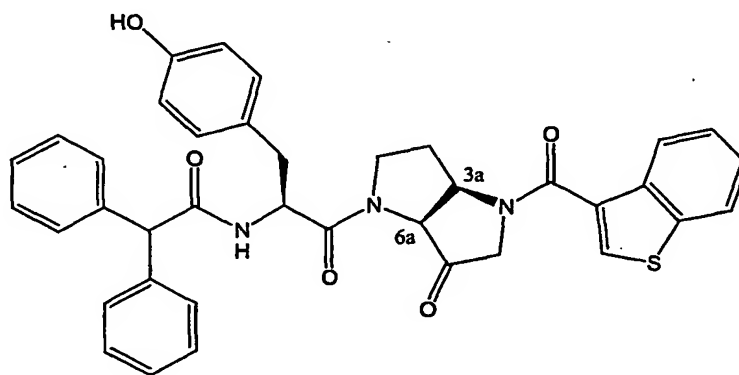
- 15 EXAMPLE 328. (3aR, 6aS)-3-Bromo-N-((1S)-1-(4-hydroxy-benzyl)-2-[4-(4-methyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl)-benzamide

-488-



HPLC Rt = 13.8-14.9 mins (> 90%), HPLC-MS 590.0 / 592.0 [M + H]⁺.

- 5 EXAMPLE 329. (3aR, 6aS)-N-[(1S)-2-[4-(Benzo[b]thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-2,2-diphenyl-acetamide



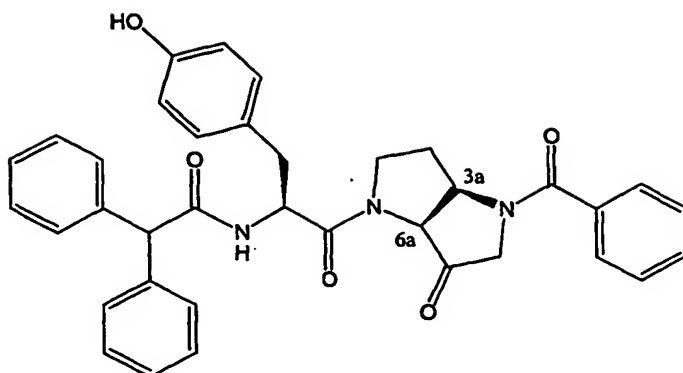
10

HPLC Rt = 17.0-18.5 mins (> 80%), HPLC-MS 644.1 [M + H]⁺.

- EXAMPLE 330. (3aR, 6aS)-N-[(1S)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b] pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-2,2-diphenyl-acetamide

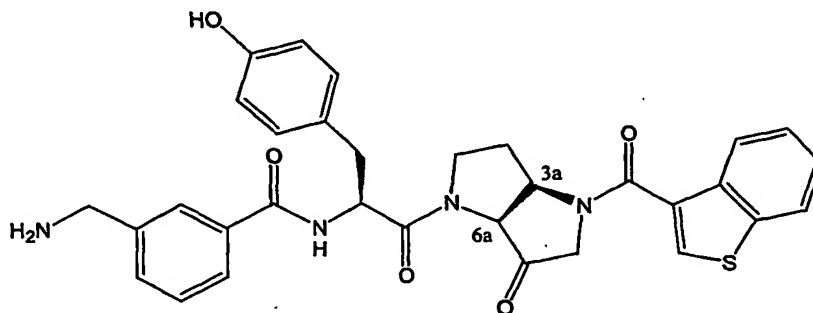
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-489-



HPLC Rt = 16.4-17.5 mins (> 85%), HPLC-MS 588.2 [M + H]⁺.

- 5 EXAMPLE 331. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-[(1*S*)-2-[4-(benzo[*b*]thiophene-3-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-benzamide

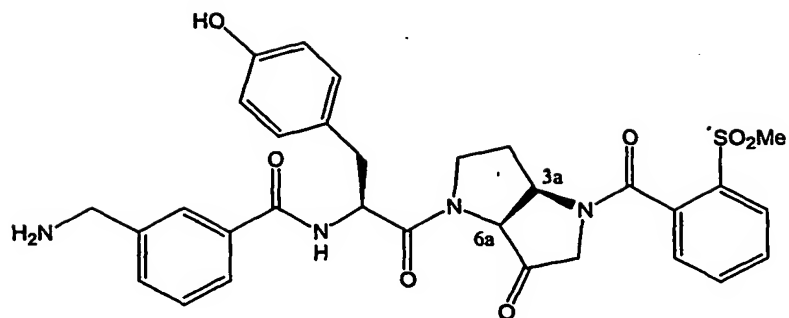


10

HPLC Rt = 10.82 mins (> 90%), HPLC-MS 583.1 [M + H]⁺.

- 15 EXAMPLE 332. (3a*R*, 6a*S*)-3-Aminomethyl-*N*-{(1*S*)-1-(4-hydroxy-benzyl)-2-[4-(2-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-benzamide

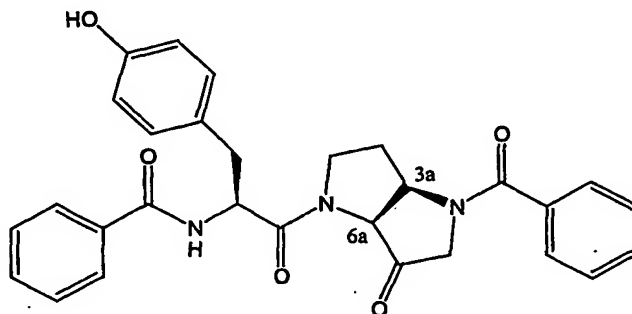
-490-



HPLC Rt = 8.16 mins (> 85%), HPLC-MS 605.1 [M + H]⁺, 623.2 [M + H + H₂O]⁺.

5

EXAMPLE 333. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-benzamide

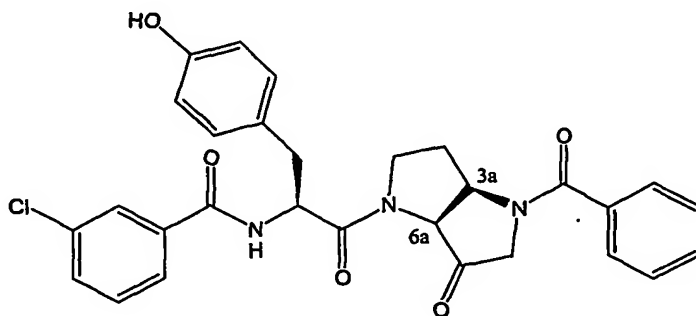


10

HPLC Rt = 11.79 mins (> 95%), HPLC-MS 498.1 [M + H]⁺.

EXAMPLE 334. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-3-chloro-benzamide

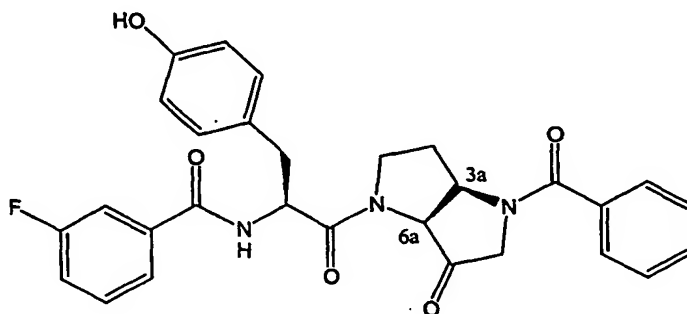
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-491-

HPLC Rt = 13.64 mins (> 95 %), HPLC-MS 532.1 / 534.1 [M + H]⁺.

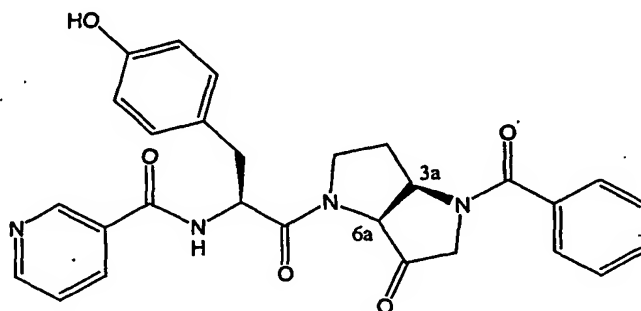
5 EXAMPLE 335. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-3-fluoro-benzamide



HPLC Rt = 12.10 mins (> 90%), HPLC-MS 516.1 [M + H]⁺.

10

EXAMPLE 336. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-nicotinamide



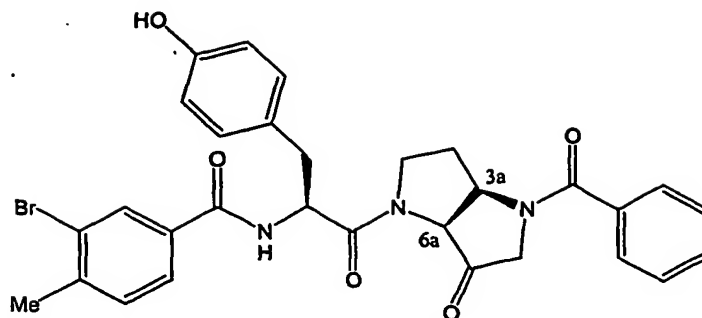
15

HPLC Rt = 8.16 mins (> 95%), HPLC-MS 499.1 [M + H]⁺, 997.2 [2M + H]⁺.

EXAMPLE 337. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-3-bromo-4-methyl-benzamide

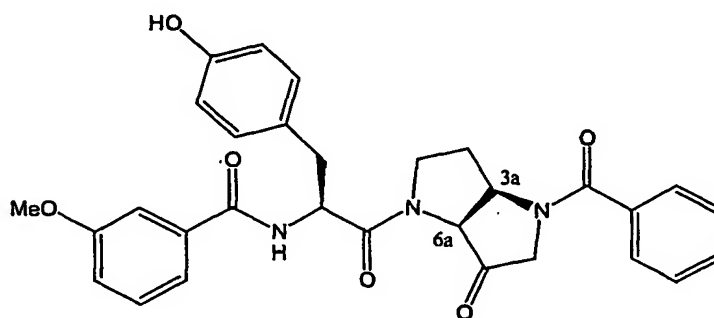
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-492-



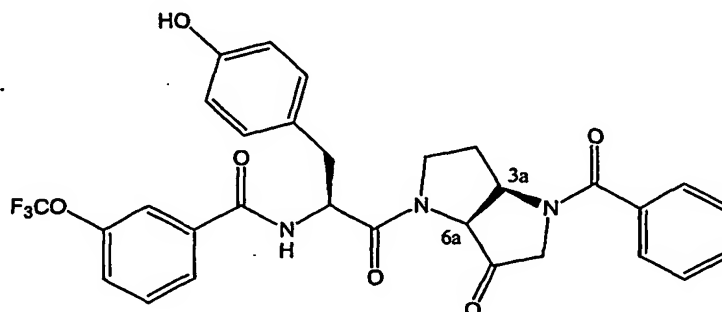
HPLC Rt = 14.0-15.1 mins (> 85%), HPLC-MS 590.0 / 592.0 $[M + H]^+$.

- 5 EXAMPLE 338. (3aR, 6aS)-N-[(1S)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b] pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-3-methoxy-benzamide



- 10 HPLC Rt = 11.81 mins (> 95%), HPLC-MS 528.1 $[M + H]^+$.

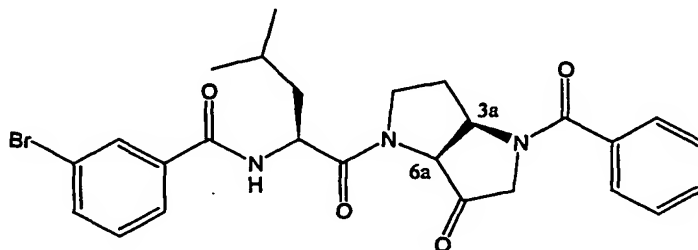
- EXAMPLE 339. (3aR, 6aS)-N-[(1S)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b] pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-3-trifluoromethoxy-benzamide



-493-

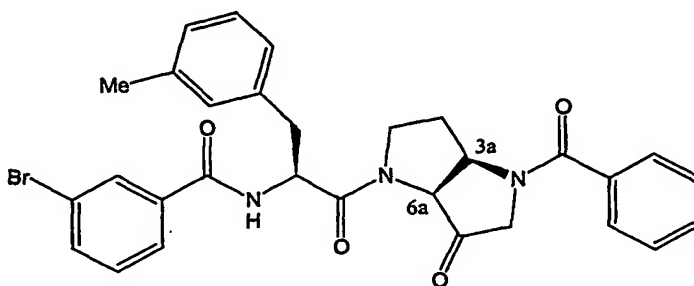
HPLC Rt = 14.21 mins (> 90%), HPLC-MS 582.1 [M + H]⁺, 600.2 [M + H + H₂O]⁺.

EXAMPLE 340. (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-
5 *b*] pyrrole-1-carbonyl)-3-methyl-butyl]-3-bromo-benzamide



HPLC Rt = 15.0-16.1 mins (> 85%), HPLC-MS 526.1 / 528.1 [M + H]⁺.

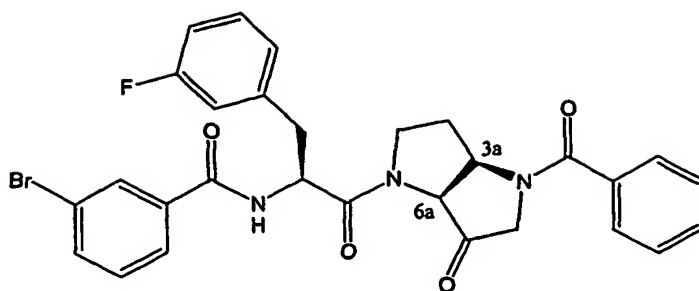
EXAMPLE 341. (3aR, 6aS)-N-[(1S)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-b] pyrrol-1-yl)-1-(3-methyl-benzyl)-2-oxo-ethyl]-3-bromo-benzamide



15 HPLC Rt = 17.0-18.3 mins (> 85%), HPLC-MS 574.0 / 576.0[M + H]⁺.

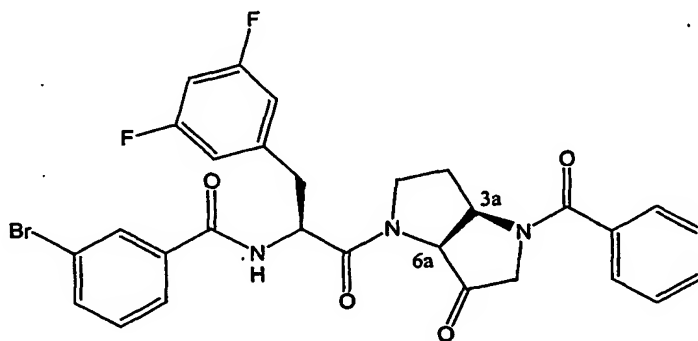
EXAMPLE 342. (3*aR*, 6*aS*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-(3-fluoro-benzyl)-2-oxo-ethyl]-3-bromo-benzamide

-494-



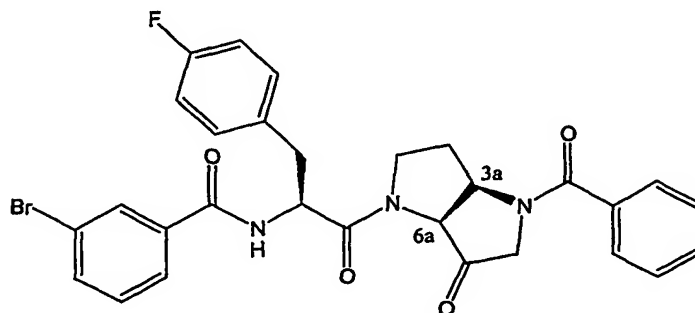
HPLC Rt = 15.8-17.1 mins (> 90%), HPLC-MS 578.0 / 580.0 [M + H]⁺.

- 5 EXAMPLE 343. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-(3,5-difluoro-benzyl)-2-oxo-ethyl]-3-bromo-benzamide



- 10 HPLC Rt = 15.9-17.3 mins (> 90%), HPLC-MS 596.0 / 598.0 [M + H]⁺.

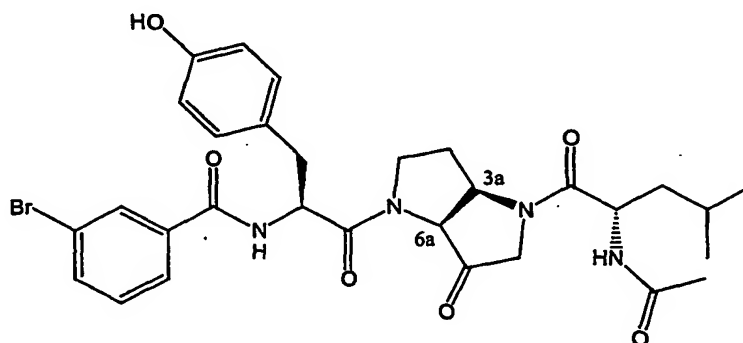
EXAMPLE 344. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-(4-fluoro-benzyl)-2-oxo-ethyl]-3-bromo-benzamide



-495-

HPLC Rt = 17.1-18.2 mins (> 90%), HPLC-MS 578.0 / 580.0 [M + H]⁺.

EXAMPLE 345. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-[4-((2*S*)-2-Acetylamino-4-methyl-
 pentanoyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-1-(4-hydroxy-benzyl)-2-
 5 oxo-ethyl]-3-bromo-benzamide



HPLC Rt = 12.73 mins (> 90%), HPLC-MS 627.0 / 629.0 [M + H]⁺.

10

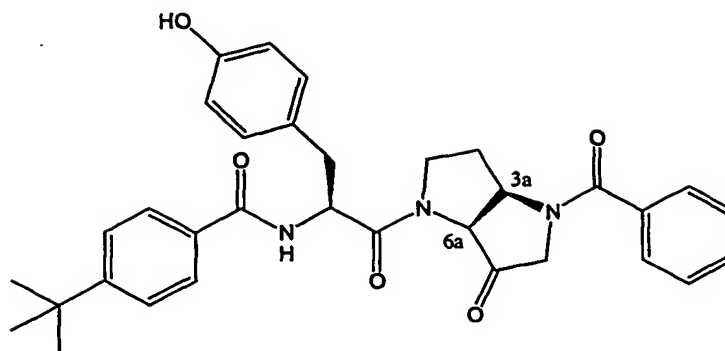
In addition, EXAMPLES 7, 8, 9, 10, 12, 14, 15, 16, 17, 18, 28, 31, 37, 59, 63, 65,
 68, 73, 85, 86, 87, 88, 89, 90, 91, 92, 93, 98, 103, 104, 111, 113, 117, 118, 145,
 151, 154, 158, 159, 161, 164, 170, 171, 172, 173, 174, 175, 178, 179, 180, 181,
 182, 185, 193, 194, 204, 216, 244, 245, 246, 247, 249a, 249b, 249c, 250, 251,
 15 254, 255, 256, 258, 259, 261, 262, 268, 269, 270, 271, 272, 273, 275, 278, 280,
 281, 282, 285, 286, 287, 288, 289, 290, 291, 292, 293, 295, 346, 356, 357, 358
 and 359 have utility as inhibitors of cathepsin L with K_i less than 5000nM.

EXAMPLES 346 to 359 were prepared as detailed for EXAMPLES 1 and 119,
 20 substituting the appropriate carboxylic acids as required and are inhibitors of
 cruzain and cruzipains with K_i ranging from 10-5000nM;

EXAMPLE 346. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-
 . *b*] pyrrol-1-yl)-1-(4-hydroxybenzyl)-2-oxo-ethyl]-4-*tert*-butyl-benzamide

25

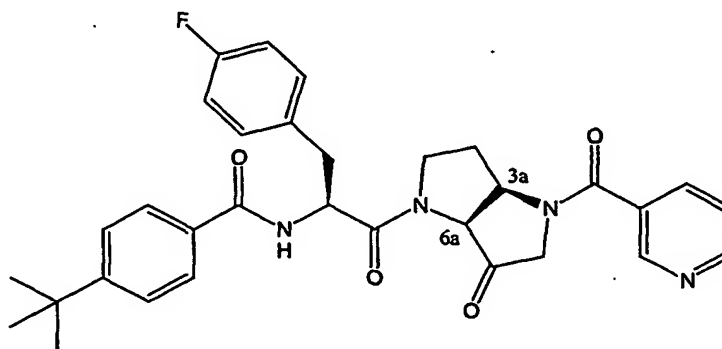
-496-



HPLC Rt = 16.0-17.1 mins (> 90%), HPLC-MS 554.3 $[M + H]^+$, 1129.5 $[2M + Na]^+$.

5

EXAMPLE 347. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide



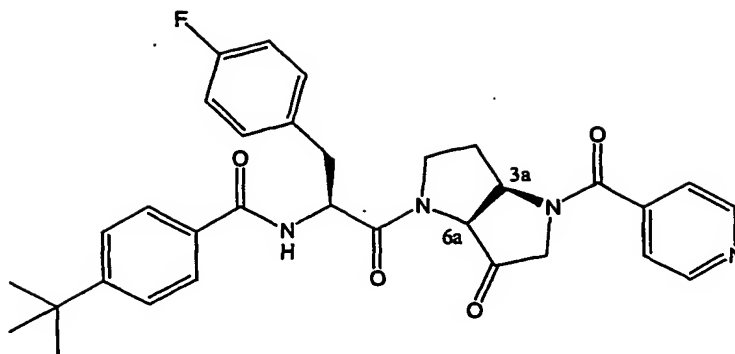
10

HPLC Rt = 16.82 mins (> 90%), HPLC-MS 557.2 $[M + H]^+$.

EXAMPLE 348. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-1-(4-fluoro-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide

15

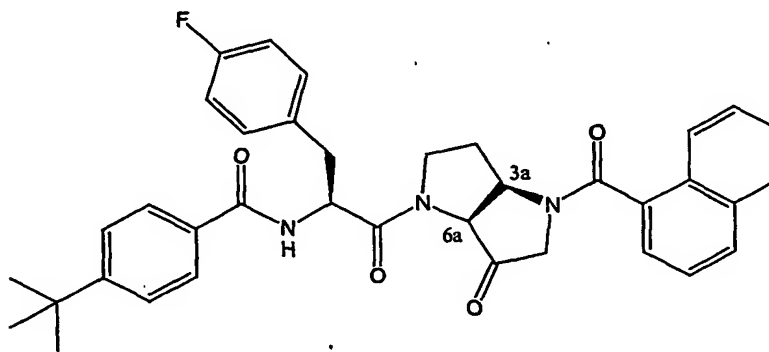
-497-



HPLC Rt = 16.44 mins (> 85%), HPLC-MS 557.2 [M + H]⁺, 575.3 [M + H + H₂O]⁺.

5

EXAMPLE 349. (3aR, 6aS)-4-*tert*-Butyl-*N*-{[(1*S*)-1-(4-fluoro-benzyl)-2-[4-(naphthalene-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl]}-benzamide



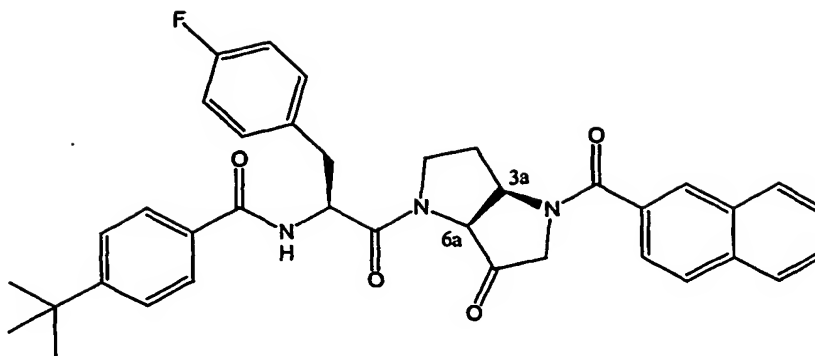
10

HPLC Rt = 19.6-20.8 mins (> 80%), HPLC-MS 606.1 [M + H]⁺.

EXAMPLE 350. (3aR, 6aS)-4-*tert*-Butyl-*N*-{[(1*S*)-1-(4-fluoro-benzyl)-2-[4-(naphthalene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl]}-benzamide

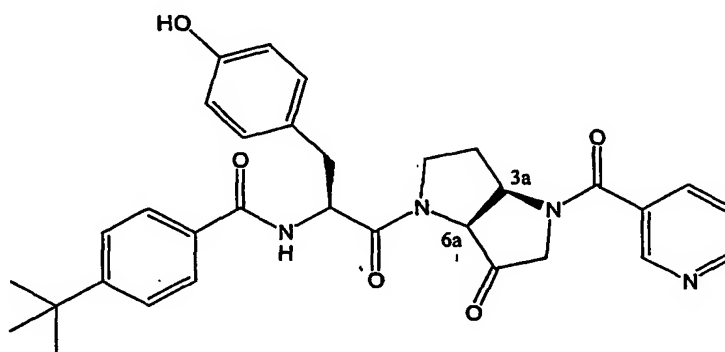
15

-498-



HPLC Rt = 21.0-22.0 mins (> 85%), HPLC-MS 606.1 [M + H]⁺.

- 5 EXAMPLE 351. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-3-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide

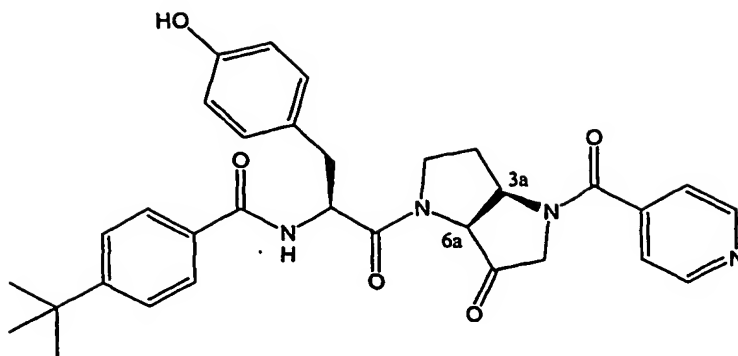


10

HPLC Rt = 14.27 mins (> 85%), HPLC-MS 555.3 [M + H]⁺, 573.3 [M + H + H₂O]⁺.

- 15 EXAMPLE 352. (3a*R*, 6a*S*)-4-*tert*-Butyl-*N*-{(1*S*)-1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(pyridine-4-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide

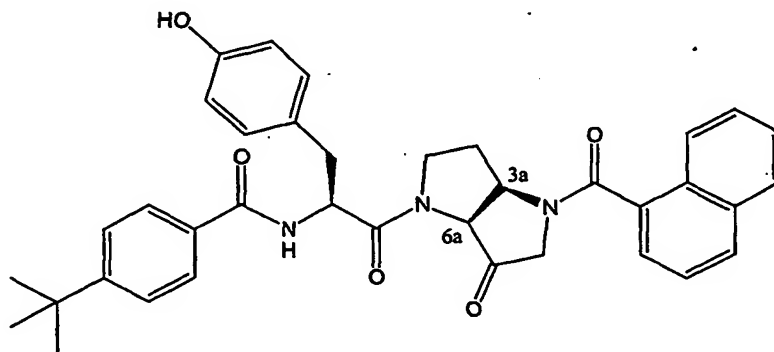
-499-



HPLC Rt = 14.35 mins (> 90%), HPLC-MS 555.2 $[M + H]^+$, 573.3 $[M + H + H_2O]^+$.

5

EXAMPLE 353. (3aR, 6aS)-4-*tert*-Butyl-*N*-{(1*S*)-1-(4-hydroxy-benzyl)-2-[4-(naphthalene-1-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-benzamide



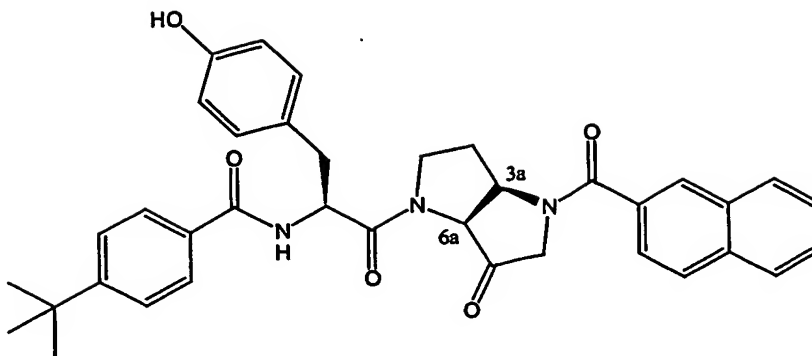
10

HPLC Rt = 17.8-18.7 mins (> 85%), HPLC-MS 604.2 $[M + H]^+$.

15

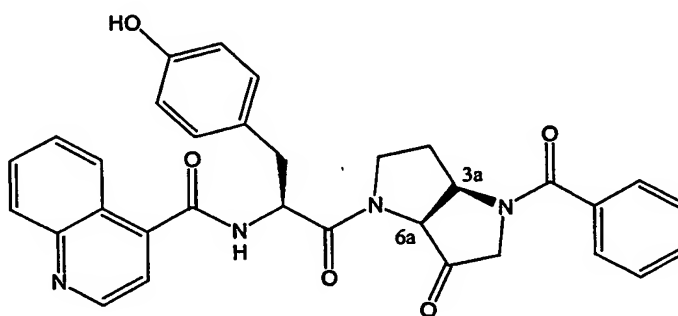
EXAMPLE 354. (3aR, 6aS)-4-*tert*-Butyl-*N*-{(1*S*)-1-(4-hydroxy-benzyl)-2-[4-(naphthalene-2-carbonyl)-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-2-oxo-ethyl}-benzamide

-500-



HPLC Rt = 17.3-18.2 mins (> 85%), HPLC-MS 604.1 [M + H]⁺.

- 5 EXAMPLE 355. (3a*R*, 6a*S*)-Quinoline-4-carboxylic acid [(1*S*)-2-(4-benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-amide

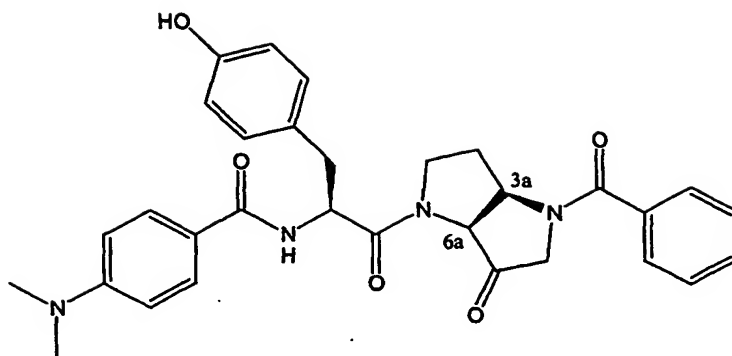


10

HPLC Rt = 10.10 mins (> 90%), HPLC-MS 549.2 [M + H]⁺, 567.2 [M + H + H₂O]⁺.

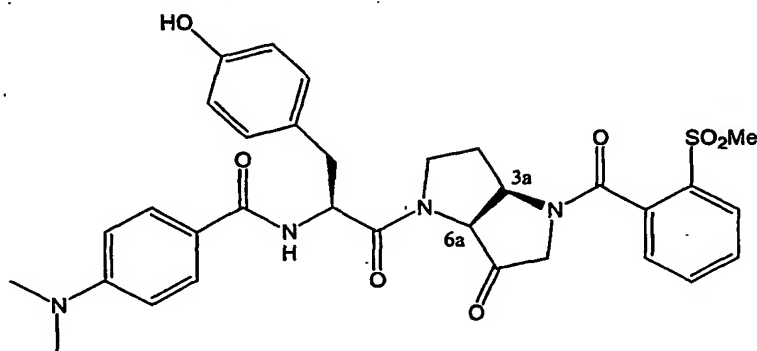
- 15 EXAMPLE 356. (3a*R*, 6a*S*)-*N*-[(1*S*)-2-(4-Benzoyl-6-oxo-hexahydro-pyrrolo[3,2-*b*] pyrrol-1-yl)-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-4-dimethylamino-benzamide

-501-



HPLC Rt = 10.34 mins (> 90%), HPLC-MS 541.2 [M + H]⁺.

- 5 EXAMPLE 357. (3aR, 6aS)-4-Dimethylamino-N-((1S)-1-(4-hydroxy-benzyl)-2-[4-(2-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl)-benzamide

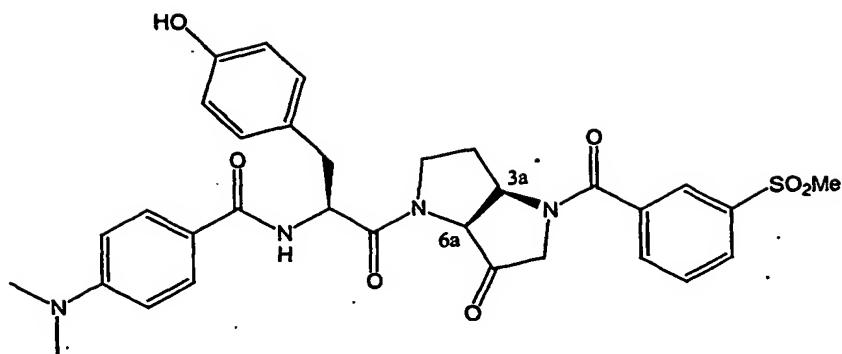


10

HPLC Rt = 9.78 mins (> 90%), HPLC-MS 619.2 [M + H]⁺, 637.2 [M + H + H₂O]⁺.

- 15 EXAMPLE 358. (3aR, 6aS)-4-Dimethylamino-N-((1S)-1-(4-hydroxy-benzyl)-2-[4-(3-methanesulfonyl-benzoyl)-6-oxo-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl]-2-oxo-ethyl)-benzamide

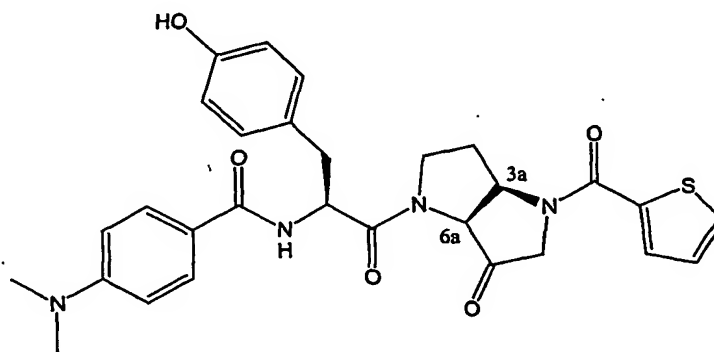
-502-



HPLC Rt = 9.95 mins (> 80%), HPLC-MS 619.2 [M + H]⁺, 637.2 [M + H + H₂O]⁺.

5

EXAMPLE 359. (3a*R*, 6a*S*)-4-Dimethylamino-*N*-{(1*S*)-1-(4-hydroxy-benzyl)-2-oxo-2-[6-oxo-4-(thiophene-2-carbonyl)-hexahydro-pyrrolo[3,2-*b*]pyrrol-1-yl]-ethyl}-benzamide



10

HPLC Rt = 10.69 mins (> 85%), HPLC-MS 547.2 [M + H]⁺, 565.2 [M + H + H₂O]⁺.

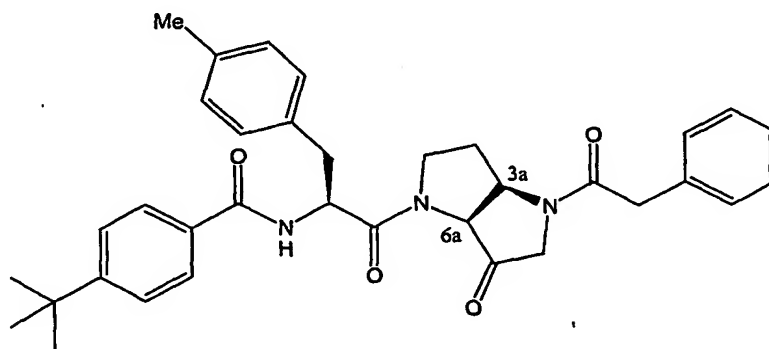
15 In addition, EXAMPLES 1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 42, 43, 44, 46, 47, 48, 49, 50, 51, 53, 54, 55, 56, 58, 59, 60, 61, 62, 63, 64, 65, 66, 68, 69, 70, 71, 72, 73, 74, 77, 79, 80, 81, 82, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 111, 113, 114, 115, 116, 117, 118, 128, 130, 20 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 145, 147, 150, 151, 154,

-503-

156, 157, 158, 159, 160, 161, 162, 164, 165, 166, 167, 168, 170, 171, 172, 173,
174, 175, 180, 183, 184, 185, 190, 191, 192, 193, 194, 196, 197, 199, 200, 203,
204, 205, 206, 207, 208, 209, 210, 212, 214, 216, 217, 218, 220, 221, 223, 224,
226, 227, 228, 233, 235, 238, 240, 241, 242, 244, 245, 246, 247, 248, 249a, 249b,
5 249c, 254, 255, 256, 260, 261, 271, 286, 287, 288, 290, 292, 295, 296, 297, 298,
299, 300, 301, 302, 303, 304, 305, 307, 308, 309, 313, 314, 315, 316, 317, 318,
319, 321, 322, 323, 324, 325, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336,
337, 338, 339, 342, 343, 344 and 345 have utility as inhibitors of cruzain and
cruzipains with K_i less than 5000nM.

10
EXAMPLE 360 was prepared as detailed for EXAMPLE 1 substituting the
appropriate carboxylic acids as required and is an inhibitor of *Leishmania mexicana*
CPB protease with K_i less than 5000nM;

15
EXAMPLE 360. (3aR, 6aS)-4-tert-Butyl-N-[(1S)-1-(4-methyl-benzyl)-2-oxo-2-(6-
oxo-4-phenylacetyl-hexahydro-pyrrolo[3,2-b]pyrrol-1-yl)-ethyl]-benzamide



20
HPLC R_t = 19.5-20.6 mins (> 80%), HPLC-MS 566.3 $[M + H]^+$.

25
In addition, EXAMPLES 1, 2, 3, 5, 6, 13, 14, 16, 17, 20, 21, 24, 25, 26, 27, 28,
29, 31, 32, 34, 35, 37, 39, 42, 43, 44, 46, 47, 48, 50, 56, 57, 59, 60, 62, 63, 64, 65,
66, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 82, 85, 86, 87, 88, 89, 90, 91, 92, 93, 95,

-504-

96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 128, 130, 132, 134, 135, 136, 137, 138, 139, 141, 142, 145, 147, 148, 150, 151, 154, 158, 159, 160, 161, 164, 165, 166, 167, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 185, 190, 191, 192, 193, 194, 201, 204, 207, 208, 209, 212, 213, 214, 215, 216, 220, 230, 233, 234, 235, 245, 246, 247, 248, 249a, 249b, 249c, 271, 278, 286, 295, 314, 315, 316, 318, 319, 329, 330, 331, 332 and 345 have utility as inhibitors of *Leishmania mexicana* CPB protease with K_i less than 5000nM.

In addition, EXAMPLES 2, 7, 14, 15, 27, 28, 31, 34, 35, 39, 40, 41, 43, 46, 48, 54, 57, 58, 59, 60, 61, 73, 74, 77, 87, 90, 91, 99, 102, 103, 104, 113, 135, 141, 151, 158, 166, 173, 194, 247, 249a, 249b, 249c, 251, 252, 253, 254, 255, 258, 259, 261, 262, 264, 266, 267, 269, 271, 273, 275, 279, 281, 286, 290, 292, 296, 298, 299, 300, 301, 304, 305, 307, 308, 309, 310, 314, 315, 316, 323, 325, 327, 329 and 330 have utility as inhibitors of cathepsin B with K_i less than 5000nM.

Solution Phase Syntheses

Alternative strategies to the solid phase techniques described for EXAMPLES 1 → 360 above are broadly outlined in Schemes 15, 17 and 18. Here, building blocks may be prepared for solution phase syntheses for example 3-Oxo-hexahydro-pyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester (analogue of compound 53, Scheme 15), prepared in 7 steps as follows:

(1) Preparation of (2*S*, 3*S*) 3-Hydroxypyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester.

Boc anhydride (2.95 g, 13.5 mmol) was added to a stirred solution of the (2*S*, 3*S*)-3-hydroxypyrrolidine-2-carboxylic acid (1.61 g, 12.3 mmol) and sodium carbonate (1.3 g, 12.3 mmol) in a mixture of dioxane (25 ml) and water (12.3 ml). The mixture was stirred for 1.5 h at ambient temperature then evaporated under reduced pressure to afford a residue (~10 ml). The

-505-

residue was diluted with water (30 ml) then extracted with ethyl acetate (40 ml). The aqueous phase was acidified (pH ~ 2.5) with dilute aqueous hydrochloric acid (0.1 M) then extracted with chloroform (4 x 50 ml). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to afford (2*S*, 3*S*)-3-hydroxypyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester as a white crystalline solid (2.39 g, ~85%), HPLC-MS (single main peak, 254.1 [M + Na]⁺ and 485.2 [M + H]⁺).

(2) Preparation of (2*S*, 3*S*) 3-Hydroxypyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-*tert*-butyl ester

A solution of allyl bromide (26 ml, 301 mmol) and tricaprilmethylammonium chloride (38.4 ml, 86.1 mmol) in dichloromethane (307 ml) was added to a stirred solution of (2*S*, 3*S*) 3-hydroxypyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (19.89 g, 86.1 mmol) and sodium hydrogen carbonate (7.23 g, 86.1 mmol) in water (307 ml). The biphasic mixture was vigorously stirred overnight then diluted with water (100 ml) and the product extracted into dichloromethane (3 x 200 ml). The combined organic layers were dried (Na₂SO₄) and evaporated under reduced pressure to afford a residue. Flash chromatography of the residue over silica gel (400 g) using ethyl acetate : heptane (1 : 4) as the eluent afforded (2*S*, 3*S*) 3-hydroxypyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-*tert*-butyl ester (9.4 g, 40 %), TLC (single spot, *R*_f = 0.28, 50% ethyl acetate in heptane), HPLC-MS (single main peak, 294.1 [M + Na]⁺, 565.3 [2M + Na]⁺); δ_H (400 MHz, CDCl₃) 1.41 and 1.46 (combined integration 9H, 2 x s, C(CH₃)₃ of geometric isomers), 1.87-1.97 (1H, m, 4-H), 2.06-2.18 (1H, m, 4-H), 2.28-2.36 (1H, m, OH), 3.55-3.71 (2H, m, 5-H₂), 4.20 and 4.32 (combined integration of 1H, 2 x s, 2-H geometric isomers), 4.46 (1H, br. s, 3-H), 4.57-4.73 (1H, m, OCH₂), 5.25-5.37 (2H, m, OCH₂CHCH₂) and 5.86-5.98 (1H, m, OCH₂CHCH₂); δ_C (100 MHz, CDCl₃) 28.6 and 28.7 (C(CH₃)₃), 32.5 and 32.95 (C-4), 44.5 and 44.9 (C-5), 66.2 (OCH₂), 68.3 (C-2), 74.6 and 75.7 (C-3), 80.6

-506-

(OC(CH₃)₃), 118.95 and 119.4 (OCH₂CHCH₂), 131.9 (OCH₂CHCH₂), 154.25 and 154.9 (NCO₂), 170.8 and 171.1 (CO₂Allyl).

(3) Preparation of (2*S*,3*R*) 3-Azido-pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-*tert*-butyl ester

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Diethyl azodicarboxylate (0.62 ml, 4.0 mmol) was added dropwise over 25 minutes to a stirred solution of (2*S*, 3*S*) 3-hydroxypyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-*tert*-butyl ester (895 mg, 3.3 mmol) and triphenylphosphine (1.08 g, 4.1 mmol) in tetrahydrofuran (30 ml) at 0°C under an atmosphere of argon. The solution was stirred for 5 minutes then diphenylphosphoryl azide (0.89 ml, 4.1 mmol) was added dropwise over 10 minutes. The mixture was stirred for 10 minutes at 0°C then for 24 hours at ambient temperature before removing solvents *in vacuo* to obtain a residue which was purified by flash chromatography over silica gel eluting with a gradient of heptane : ethyl acetate 3:1 → 1:1. Appropriate fractions were combined and the solvents removed *in vacuo* to obtain (2*S*, 3*R*) 3-azidopyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-*tert*-butyl ester as a colourless oil (850 mg, 88%) which was contaminated with ~5% of 4,5-dihydropyrrole-1,2-dicarboxylic acid 2-allyl ester 1-*tert*-butyl ester. TLC (main spot, R_f = 0.70, heptane : ethyl acetate 1:1), HPLC-MS 197.1 [M-Boc+H]⁺, 241.1 [M-Bu+2H]⁺, 319.2 [M+Na]⁺, 615.3 [2M + Na]⁺; δ_H (CDCl₃ at 298K); (Doubling up of peaks in spectrum due to restricted rotation around Fmoc amide bond) 1.45 and 1.49 (1.8 and 1.2H respectively, Me₃C, each s), 2.10-2.24 (2H, H-4, m), 3.44-3.52 and 3.60-3.73 (each 1H, H-5, m), 4.31-4.40 (1H, H-3, m), 4.45 and 4.54 (0.6 and 0.4H respectively, H-2, each d, *J* = 7.6Hz), 4.66-4.78 (2H, CH₂CH=CH₂, m), 5.28-5.33 (1H, CH₂CH=CH₂, m), 5.42 (1H, CH₂CH=CH₂, dd, *J* = 17.2 and 3.7Hz), 5.91-6.04 (1H, CH₂CH=CH₂); δ_C (CDCl₃ at 298K); 28.40 (u, Me₃C), 29.40/30.18 (d, C-4), 44.22/44.62 (d, C-5), 61.21/61.86/61.98/62.23 (u, C-2 and C-3), 65.81/66.10 (d, CH₂CH=CH₂),

-507-

80.76/81.24 (q, Me_3C), 118.79/119.21 (d, $\text{CH}_2\text{CH}=\text{CH}_2$), 131.82/131.87 (u, $\text{CH}_2\text{CH}=\text{CH}_2$), 153.53/154.11 (q, OCON), 169.19/169.38 (q, CO_2CH_2).

(4) Preparation of (2*S*, 3*R*) 3-Benzylloxycarbonylaminopyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-propyl ester

Palladium (10 wt. % on carbon powder, 300 mg) was added portion wise to a solution of (2*S*, 3*R*) 3-azidopyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-*tert*-butyl ester (790 mg, 2.66 mmol) in ethanol (20 ml) at 0 °C. The mixture was stirred for 2 h under an atmosphere of hydrogen at ambient temperature, then filtered over celite and concentrated *in vacuo* to afford a residue (540 mg). The residue was suspended in dioxane (6 ml) then a solution of sodium carbonate (529 mg, 5 mmol) in water (12 ml) added. The mixture was cooled to 0 °C then a solution of benzyloxy chloroformate (0.314 ml) in dioxane (6 ml) added portion wise over 40 min at 0 °C. The mixture was stirred for 30 min at 0 °C then at ambient temperature for 40 min. Water (150 ml) was added and the products extracted with chloroform (3 x 100 ml), dried (Na_2SO_4) and evaporated under reduced pressure to afford a residue. Flash chromatography of the residue over silica (100 g) using ethyl acetate : heptane (1 : 4) as the eluent afforded (2*S*, 3*R*) 3-benzyl oxycarbonylaminopyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-propyl ester (240 mg, 22 %), TLC (single spot, R_f = 0.47, 50% ethyl acetate in heptane); analytical HPLC R_t = 18.06 min, HPLC-MS (single main peak, 429.2 $[\text{M} + \text{Na}]^+$, 835.4 $[2\text{M} + \text{Na}]^+$); δ_{H} (400 MHz, CDCl_3) 0.90 (3H, t, J = 7.3 Hz, CH_3), 1.41 and 1.45 (combined integration 9H, 2 x s, $\text{C}(\text{CH}_3)_3$ of geometric isomers), 1.46-1.66 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 1.89-2.00 (1H, m, 4- H_2), 2.12-2.25 (1H, m, 4- H_2), 3.32-3.46 (1H, m, 5-H), 3.55-3.72 (1H, m, 5-H), 3.99-4.07 (1H, m, 3-H), 4.46-4.55 ($\text{OCH}_2\text{CH}_2\text{CH}_3$), 4.88-5.17 (combined integration of 3H, m, 2-H and OCH_2Ph), and 7.29-7.42 (6H, m, C_6H_5 and NH); δ_{C} (100 MHz, CDCl_3) 10.5 (CH_3), 22.10 (OCH_2CH_2), 28.41 and 28.50 ($\text{C}(\text{CH}_3)_3$), 29.4 and 30.5 (C-4), 43.9 and 44.3 (C-5), 52.8 (C-3), 60.5 and 61.3 (C-2), 66.9, 67.0 and

-508-

67.2 (OCH₂Ph and OCH₂), 80.5 (OC(CH₃)₃), 128.3, 128.4 and 128.7 (*o*-, *m*- and *p*-C₆H₅), 136.2 (NHCOOCH₂C), 153.8 and 155.7 (NCO₂ and NHCO₂) and 171.1 (CO₂Propyl).

5 (5) Preparation of (2*S*, 3*R*) 3-Benzyloxycarbonylaminopyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester

A solution of sodium hydroxide (185 mg, 4.6 mmol) in water (1.6 ml) was added to a solution of (2*S*, 3*R*) 3-benzyloxycarbonylaminopyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-propyl ester (229 mg, 0.56 mmol) in ethanol (6 ml). The mixture was stirred for 8 h at ambient temperature. Water (50 ml) was added and the ethanol removed under reduced pressure. The aqueous residue was acidified to pH = 2 by the addition of dilute aqueous hydrochloric acid (0.1 M). The mixture was then extracted with ethyl acetate (3 x 50 ml), dried (Na₂SO₄) and evaporated under reduced pressure to afford (2*S*, 3*R*) 3-benzyloxycarbonylaminopyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (200 mg, 98%), analytical HPLC *R*_t = 14.03 min, HPLC-MS (single main peak, 387.2 [M + Na]⁺, 751.4 [2M + Na]⁺); δ_H (400 MHz, CDCl₃) 1.35 and 1.37 (combined integration 9H, 2 x s, C(CH₃)₃ of geometric isomers), 1.86-2.15 (2H, m, 4-H₂), 3.14-3.71 (2H, m, 5-H₂), 4.20-4.49 (2H, m, 2-H and 3-H), 5.02-5.22 (2H, m, OCH₂Ph), and 7.18-7.37 (6H, m, C₆H₅ and NH); δ_C (100 MHz, CDCl₃) 28.3, 28.4, 28.5 and 29.2 (C(CH₃)₃ and C-4), 43.8 and 44.3 (C-5), 52.3 and 53.1 (C-3), 61.0 and 61.4 (C-2), 67.2 and 68.4 (OCH₂Ph), 80.6 and 80.8 (OC(CH₃)₃), 128.2, 128.5 and 128.6 and 128.7 (*o*-, *m*- and *p*-C₆H₅), 135.5 (NHCOOCH₂C), 153.8 and 154.3 (NCO₂), 158.6 (NHCO₂), 175.6 and 175.9 (CO₂H).

30 (6) Preparation of (2*S*, 3*R*) 3-Benzyloxycarbonylamino-2-(2-diazoacetyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester

-509-

(2*S*, 3*R*) 3-benzyloxycarbonylaminopyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (161 mg, 0.443 mmol) was dissolved with stirring in anhydrous dichloromethane (18 ml). The reaction was flushed with nitrogen and cooled to -15 °C. *iso*-Butylchloroformate (0.063 ml, 0.487 mmol) in anhydrous dichloromethane (1.5 ml) and *N*-methylmorpholine (0.097 ml, 0.886 mmol) in anhydrous dichloromethane (1.5 ml) were added simultaneously in 0.5 ml aliquots over 15 min. The mixture was stirred for 45 min at -15 °C then ethereal diazomethane [generated from addition of diazald (4.7 g, ~15 mmol) in diethyl ether (75 ml) onto sodium hydroxide (5.25 g) in water (7.5 ml) / ethanol (15 ml) at 60 °C] was added to the activated amino acid solution. The mixture was allowed to warm to ambient temperature and stirred for 24 h. A few drops of acetic acid were added to the mixture, followed by diethyl ether (200 ml). The ethereal layer was washed with saturated aqueous sodium hydrogen carbonate (80 ml), dried (Na₂SO₄) and the solvents removed under reduced pressure to give a yellow residue (300 mg). Flash chromatography of the residue over silica (35 g) using ethyl acetate : heptane (1 : 3) afforded (2*S*, 3*R*) 3-benzyloxycarbonylamino-2-(2-diazoacetyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (150 mg, 87%), TLC (single spot, *R_f* = 0.29, 50% ethyl acetate in heptane); analytical HPLC *R_t* = 15.15 min, HPLC-MS (single main peak, 411.2 [M + Na]⁺, 799.4 [2M + Na]⁺).

(7) Preparation of (2*S*, 3*R*) 3-Oxohexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester

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A solution of (2*S*, 3*R*) 3-benzyloxycarbonylamino-2-(2-diazoacetyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (90 mg, 0.23 mmol) was added over 1 h to a refluxing solution of rhodium(II) acetate dimer (2 mg, 0.0046 mmol) in dichloromethane (3 ml). The mixture was heated under reflux for 2 h and the solvent then removed *in vacuo*. The residue was diluted with tetrahydrofuran (40 ml) then filtered through a pad of celite. The filtrate was then concentrated *in vacuo* to afford a residue (106 mg).

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-510-

Flash chromatography of the residue over silica (35 g) using ethyl acetate : heptane (1 : 3) afforded (2*S*, 3*R*) 3-oxohexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester (14 mg, 17 %), TLC (two possible rotameric spots, R_f = 0.30 and 0.23, 50% ethyl acetate in heptane), analytical HPLC R_t = 15.479 min (~60 %), 16.393 (~10 %), 17.197 (~10 %), 18.085 (~10 %) and 21.665 (~10 %); HPLC-MS (4 main peaks, $361.0 = [M + H]^+$, $379 = [M + H_3O]^+$, $401.0 [M + H_2O + Na]^+$, $[2M + H]^+ = 721.0$, $[2M + Na]^+ = 743.0$, $[2(M + H_2O) + Na]^+ = 779.0$); δ_H (500 MHz, $CDCl_3$) 1.40-1.50 (9H, m, $C(CH_3)_3$), 1.78-1.86 (1H, m, NCH_2CH_2), 2.30-2.47 (1H, m, NCH_2CH_2), 3.90-4.06 (2H, m, NCH_2), 5.05-5.20 (4H, m, OCH_2 , $BocNCHCO$ and $CbzNCH$), 5.44 (1H, d, $J = 2.2$ Hz, $CbzNCH_2$), 5.56 (1H, br. s, $CbzNCH_2$) and 7.30-7.37 (5H, m, C_6H_5); δ_C (126 MHz, $CDCl_3$) 27.5 ($C(CH_3)_3$), 29.6 and 32.2 (NCH_2CH_2), 57.7 ($CbzNCH$), 59.1 (NCH_2), 67.0 (OCH_2), 77.2 ($BocNCH$), 83.5 ($OC(CH_3)_3$), 110.7 ($CbzNCH_2$), 128.0, 128.2 and 128.5 (*o*-, *m*- and *p*- C_6H_5), 136.1 (OCH_2C of Cbz), 147.6, 151.4 155.7 and 167.1 (2x NCO_2 and $CbzNCH_2CO$).

(8) Preparation of (2*S*, 3*R*) 3-Oxohexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid benzyl ester hydrochloride salt (analogue of compound 54).

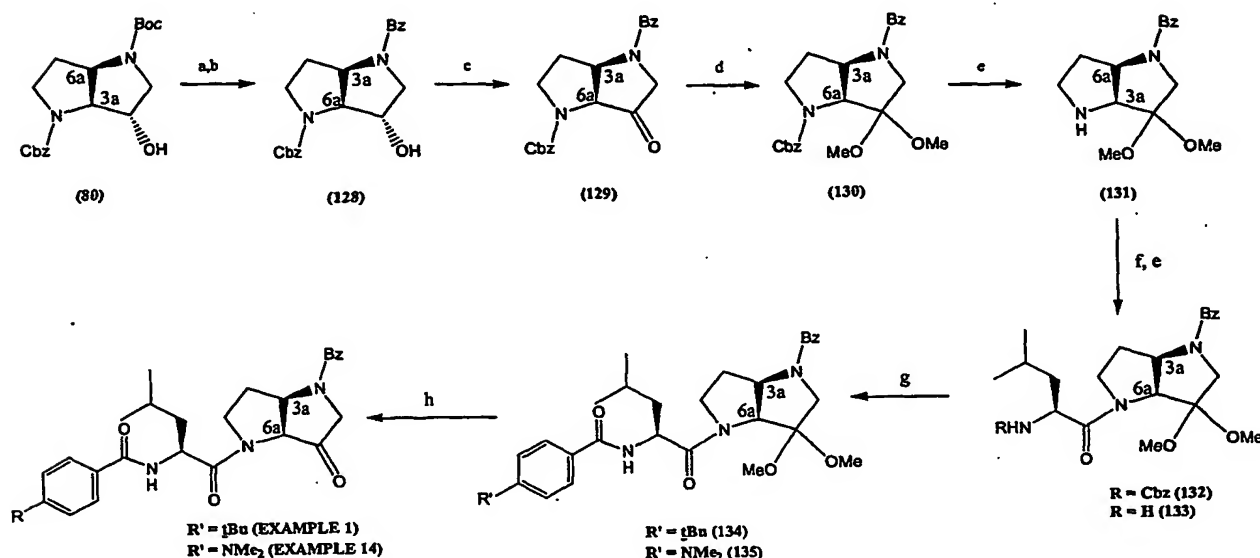
(2*S*, 3*R*) 3-oxohexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 1-benzyl ester 4-*tert*-butyl ester (9 mg, 0.025 mmol) was dissolved in 4M HCl in dioxane (1.25 ml) then stirred for 1 h at room temperature. The mixture was concentrated *in vacuo* then toluene (10 ml) added. The mixture was concentrated once again *in vacuo* and the procedure repeated to afford a residue (10 mg, ~100 %), HPLC-MS (single main peak, 261.1 $[M + H]^+$ and 279.1 $[M + H_3O]^+$).

Alternatively, a useful building block for solution phase synthesis is (3*S*, 3*aS*, 6*aR*)-3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 4-benzyl

-511-

ester 1-*tert*-butyl ester (80) described earlier in Scheme 20. The utility of building block (80) is detailed in alternative syntheses of EXAMPLES 1 and 14, through Scheme 26, which is an example of the general synthetic strategy detailed in Scheme 18.

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Scheme 26. (a) 4N HCl in 1,4-dioxane, 30mins, RT. (b) Benzoic anhydride, 4-methylmorpholine, DMF, RT, 1hr. (c) Dess-Martin periodinane, DCM. (d) Trimethylorthoformate, anhydrous MeOH, cat. *p*-TsOH, under Ar, 65°C. (e) Pd-C / H₂, ethanol / methanol. (f) 1eq Cbz-Leu-F, DMF, RT. (g) 1.05eq R-COOH, HBTU, HOBT, NMM, DMF, RT. (h) 95% Trifluoroacetic acid / 5% water, RT.

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Preparation of (3a*R*, 6*S*, 6a*S*)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid benzyl ester (128)

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A solution of HCl in 1,4-dioxane (4.0M, 11 ml, 44 mmol) was added to (3*S*, 3a*S*, 6a*R*)-3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylic acid 4-benzyl ester 1-*tert*-butyl ester (80) (450 mg, 1.24 mmol). The solution was stirred for 65 minutes whereupon a white suspension formed. The solvents were removed *in vacuo* and the residue azeotroped with diethyl ether (3x 15 ml) and then dimethylformamide (10 ml) and benzoic anhydride (295 mg, 1.31 mmol) added.

-512-

The solution was placed under an atmosphere of argon then 4-methylmorpholine (0.29 ml, 2.6 mmol) was added to the solution dropwise whilst stirring over 0.5 minutes. The mixture was stirred for 1.75 hours then the solvents were removed *in vacuo*. The residue was dissolved in ethyl acetate (100 ml) then washed with saturated aqueous sodium hydrogen carbonate solution (100 ml), pH 3 hydrochloric acid (100 ml) then brine (100 ml). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to afford (3a*R*, 6*S*, 6a*S*)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid benzyl ester (128) as a pale yellow gum (465 mg), which was used without further purification.

Analytical HPLC $R_t = 14.967$ min; HPLC-MS 367.1 $[\text{M} + \text{H}]^+$, 733.1 $[2\text{M} + \text{H}]^+$; Elemental analysis $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4 \cdot 0.4\text{EtOAc}$ req. (fnd.) % C 67.62 (67.73), % H 6.33 (6.17), % N 6.98 (7.08); HRMS $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ req. 389.1477, fnd. 389.1476 (-0.40ppm); d_H (500 MHz, CDCl_3) approximately 3 : 1 mixture of rotamers, 2.10-2.21 (1H, m, BzNCHCH_2), 2.24-2.36 (1H, m, BzNCHCH_2), 3.20-3.35 (1H, m, CbzNCH_2), 3.35-3.66 (2H, m, BzNCH_2), 3.74-3.80 (1H, m, CbzNCH_2), 4.16-4.20 (1H, m, CbzNCH), 4.38-4.42 (1H, br. s; CHOH), 4.94-5.04 (1H, m, BzNCH), 5.08-5.22 (2H, m, OCH_2Ph), 7.30-7.52 (10H, aromatic CH); d_C (125 MHz, CDCl_3) 31.02, 30.40 (BzNCHCH_2), 45.73, 45.86 (CbzNCH_2), 56.43, 56.74 (BzNCH_2), 60.58, 61.49 (BzNCH), 66.68, 67.33 (OCH_2Ph), 66.92, 67.76 (CbzNCH), 73.01, 73.86 (CHOH), 126.77, 127.48, 127.99, 128.23, 128.28, 128.45, 128.56, 128.87, 130.02, 130.38 and 134.53 (CH aromatics), 136.16, 136.23, 136.33 (aromatic quaternary), 154.26, 154.97 (CbzC=O), 170.06, 171.19 (BzC=O).

25 Preparation of (3a*R*, 6a*S*)-4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid benzyl ester (129)

(3a*R*, 6*S*, 6a*S*)-4-Benzoyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid benzyl ester (128) (0.78 g, 2.13 mmol) was dissolved in dichloromethane (20 ml) with stirring under argon. Dess-Martin periodinane (1.804 g, 4.26 mmol) was added and the mixture stirred for 16 hours. The mixture was concentrated *in vacuo* and the residue purified by flash chromatography over silica, eluting with

-513-

ethyl acetate : heptane mixtures to give (3a*R*, 6a*S*)-4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*] pyrrole-1-carboxylic acid benzyl ester (129) (0.61 g, 78%) as an off-white gum. TLC (R_f = 0.27, EtOAc : heptane 3 : 1), analytical HPLC single main peak, R_t = 14.65-16.30 min., HPLC-MS 365.1 $[M + H]^+$, 383.1 $[M + H + H_2O]^+$; Elemental analysis $C_{21}H_{20}N_2O_4 \cdot 1.2H_2O$ req.(*find.*) % C 65.38 (65.12), % H 5.85 (5.65), % N 7.26 (6.95); HRMS $C_{21}H_{20}N_2O_4Na$ req. 387.1321, *find.* 387.1324 (0.76ppm); δ_c (125 MHz, $CDCl_3$) 30.41, 30.89, 31.23 ($BzNCHCH_2$), 45.75 ($CbzNCH_2$), 54.55, 63.04 ($BzNCH + CbzNCH$), 57.91, 58.45, 58.99, 59.73 ($BzNCH_2$), 67.60, 68.07 (OCH_2Ph), 127.00, 127.38, 127.48, 127.98, 128.11, 128.48, 128.62, 128.74, 130.48, 130.83 (CH aromatics), 135.07, 136.14 (quaternary aromatics), 154.54, 155.03 ($CbzCO_2$), 170.58 ($BzCO$), 204-207 (broad, $C=O$).

Preparation of (3a*R*, 6a*S*)-4-benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*] pyrrole-1-carboxylic acid benzyl ester (130)

(3a*R*, 6a*S*)-4-Benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid benzyl ester (129) (0.60 g, 1.65 mmol) was dissolved in methanol (10 ml) with stirring. Trimethylorthoformate (1.8 ml, 16.5 mmol) was added followed by *para*-toluenesulfonic acid (40 mg) and the mixture heated under argon at 65 °C for 16 hours. The mixture was reduced *in vacuo* to leave a dark oil (0.8 g). Flash chromatography over silica, eluting with ethyl acetate : heptane mixtures gave (3a*R*, 6a*S*)-4-benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid benzyl ester (130) (0.52 g, 77%) as a fine white crystalline solid. TLC (R_f = 0.40, EtOAc : heptane 3 : 1), analytical HPLC single main peak, R_t = 18.22 min., HPLC-MS 411.1 $[M + H]^+$, 433.1 $[M + Na]^+$, 843.1 $[2M + Na]^+$; HRMS $C_{23}H_{26}N_2O_5Na$ req. 433.1739, *find.* 433.1727 (-2.94ppm); δ_H (500 MHz, $CDCl_3$) 1.96-2.07, 2.15-2.22 (2H, m, $BzNCHCH_2$), 3.04-3.42 (6H, m, 2x OCH_3), 3.25 (1H, m, $CbzNCH_2$), 3.4 (1H, m, $BzNCH_2$), 3.58-3.67 (1H, m, $BzNCH_2$), 3.96-4.07 (1H, m, $CbzNCH_2$), 4.35-4.58 (1H, m, $CbzNCH$), 4.98-5.26 (3H, $BzNCH + OCH_2Ph$), 7.28-7.49 (10H aromatics); δ_c (125 MHz, $CDCl_3$) 32.27, 32.59 ($BzNCHCH_2$), 46.74 ($CbzNCH_2$), 49.36, 51.10, 51.59 (2x OCH_3), 54.59, 56.08

-514-

(BzN $\underline{\text{CH}}_2$), 60.77, 61.08 (BzN $\underline{\text{CH}}$), 62.47 (CbzN $\underline{\text{CH}}$), 67.28 (O $\underline{\text{CH}}_2$ Ph), 106.76, 107.02 ($\underline{\text{C}}$ (OCH $_3$) $_2$), 126.84, 127.35, 127.90, 128.06, 128.39, 130.05, 130.38 ($\underline{\text{CH}}$ aromatics), 135.91, 136.48 (quaternary aromatics), 155.44 (Cbz $\underline{\text{CO}}_2$), 169.54 (Bz $\underline{\text{CO}}$).

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Preparation of (3a*S*, 6a*R*)-(3,3-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrol-1-yl)phenylmethanone (131)

Methanol (15 ml) was added cautiously dropwise to a stirred mixture of (3a*R*, 6a*S*)-4-benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid benzyl ester (130) (0.48 g, 1.17 mmol) and 10% palladium on charcoal (100 mg) at 0 °C under an atmosphere of argon over 10 minutes. The argon was then replaced by an atmosphere of hydrogen and stirring continued at ambient temperature for 85 minutes before replacing the hydrogen with argon and adding ethanol (30 ml). The mixture was filtered under reduced pressure through celite and the filter cake washed with methanol (25 ml) then ethanol (70 ml). Solvents were removed from the filtrate *in vacuo* to obtain (3a*S*, 6a*R*)-(3,3-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrol-1-yl) phenylmethanone (131) as a colourless oil (340 mg), which was used without further purification. HPLC-MS 277.1 [M + H] $^+$, 553.2 [2M + H] $^+$.

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Preparation of (3a*R*, 6a*S*)-[(1*S*)-1-(4-benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]carbamic acid benzyl ester (132)

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(i) Preparation of Cbz-L-Leucine Fluoride

Cbz-L-Leucine (1.115 g, 4.2 mmol) was dissolved in dichloromethane (50 ml) with stirring under argon. (Diethylamino)sulfur trifluoride (DAST, 792 μ l, 6.0 mmol) was added and the mixture stirred for 40 minutes. Ice-cooled water (200 ml) was added to the mixture and the organic layer separated, dried (Na $_2$ SO $_4$) and reduced *in vacuo* to a mobile tan oil (1.14 g). An analytical sample, pre-treated with 10% pyridine in methanol for 15 minutes gave HPLC-MS 266.1 [M + H] $^+$

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-515-

(acid, < 5%), 280.1 $[M + H]^+$, 302.1 $[M + Na]^+$, 581.1 $[2M + Na]^+$ (methyl ester, ~ 95%).

(ii) Crude (3a*S*, 6a*R*)-(3,3-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrol-1-yl)phenyl methanone (131) (~ 1.17 mmol) was dissolved in anhydrous dimethylformamide (5 ml) with stirring. Cbz-L-Leucine fluoride (0.33 g, 1.23 mmol) was added and the mixture stirred under argon for 1 hour. The mixture was reduced *in vacuo* to a semi-mobile dark oil (~ 1.0 g). Flash chromatography over silica, eluting with ethyl acetate : heptane mixtures gave (3a*R*, 6a*S*)-[(1*S*)-1-(4-benzoyl-6,6-dimethoxyhexahydro pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]carbamic acid benzyl ester (132) (0.55 g, 90%) as an off-white crystalline solid. TLC (R_f = 0.35, EtOAc : heptane 3 : 1), analytical HPLC single main peak, R_t = 19.396 min., HPLC-MS 524.1 $[M + H]^+$, 546.1 $[M + Na]^+$, 1069.2 $[2M + Na]^+$; Elemental analysis $C_{29}H_{37}N_3O_6$ req.(*find.*) % C 66.52 (66.26), % H 7.12 (7.30), % N 8.02 (7.86); HRMS $C_{29}H_{37}N_3O_6Na$ req. 546.2580, *find.* 546.2584 (0.67ppm); δ_H (500 MHz, $CDCl_3$) 0.92-1.04 (6H, m, 2x Leu δCH_3), 1.45-1.55 (2H, m, Leu βCH_2), 1.73-1.84 (1H, m, Leu γCH), 1.92-1.99, 2.10-2.16, 2.22-2.30 (2H, 4 : 6 : 10, m, BzNCHCH₂), 2.94, 3.19, 3.23 and 3.40 (6H total, each s, C(OCH₃)₂), 3.14-3.38 (2H, m, 1x BzNCH₂ and 1x CbzLeuNCH₂), 3.60-3.68 (1H, 4 : 6, each d, J = 12 Hz, 1x BzNCH₂), 4.03-4.10, 4.11-4.18 (1H, 4 : 6, m, 1x CbzLeuNCH₂), 4.33 (0.4H, d, J = 6.3 Hz, 0.4x CbzLeuNCH), 4.5-4.65 (0.6H, m, 0.6x Leu αCH), 4.82 (0.6H, d, J = 6.45 Hz, 0.6x CbzLeuNCH), 4.87-4.93 (0.4H, m, 0.4x Leu αCH), 5.0-5.14 (3H, m, BzNCH + OCH₂Ph), 5.42 (0.6H, d, J = 8.3 Hz, LeuNH), 5.57 (0.4H, d, J = 8.9 Hz, LeuNH), 7.3-7.5 (10H, aromatics); δ_C (125 MHz, $CDCl_3$) 21.99, 22.20, 22.67, 23.06, 23.67 (2x Leu $\delta \underline{C}H_3$), 24.37, 24.57 (Leu $\gamma \underline{C}H$), 31.58, 31.86, 33.26 (BzNCHCH₂), 42.78 (Leu $\beta \underline{C}H_2$), 44.12, 45.79, 47.05 (CbzLeuNCH₂), 49.31, 49.99 (1x OCH₃), 51.18, 51.27, 51.30, 51.47 (1x OCH₃ + Leu $\alpha \underline{C}H$), 55.55, 57.03 (BzNCH₂), 59.69, 61.32 (BzNCH), 60.30, 61.04 (CbzLeuNCH), 66.39, 66.88(OCH₂Ph), 106.27, 107.11 ($\underline{C}(\text{OCH}_3)_2$), 126.84, 127.32, 127.42, 127.87, 127.94, 128.09, 128.43, 128.48, 130.18, 130.43, 130.50

-516-

(CH aromatics), 135.68, 135.81, 136.28, 136.73 (quaternary aromatics), 155.58, 156.21 (CbzC=O), 169.56, 169.62 (BzC=O), 172.35, 173.36 (Leu C=O).

**Preparation of (2*S*, 3*aR*, 6*aS*)-2-amino-1-(4-benzoyl-6,6-dimethoxyhexahydro
pyrrolo[3,2-*b*]pyrrol-1-yl)-4-methylpentan-1-one (133)**

Methanol (15 ml) was added cautiously dropwise to 10% palladium on charcoal (75 mg) at 0 °C under an atmosphere of argon over 10 minutes whilst stirring followed by a solution of (3*aR*, 6*aS*)-[(1*S*)-1-(4-benzoyl-6,6-dimethoxy hexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]carbamic acid benzyl ester (132) (0.52 g, 0.99 mmol) in methanol (15 ml). The argon was then replaced by an atmosphere of hydrogen and stirring continued at ambient temperature for 5.5 hours. A suspension of 10% palladium on charcoal (15 mg) in methanol (1 ml) was added and stirring continued for 2.25 hours. The hydrogen was replaced by argon then ethanol (100 ml) was added before filtering the mixture through celite. The filter cake was washed with ethanol (100 ml) then the filtrate separated into two equal portions before concentrating separately *in vacuo* to obtain two identical batches of (2*S*, 3*aR*, 6*aS*)-2-amino-1-(4-benzoyl-6,6-dimethoxy hexahydropyrrolo[3,2-*b*]pyrrol-1-yl)-4-methyl pentan-1-one (133). TLC (Single spot, R_f = 0.05, EtOAc : heptane 9 : 1), HPLC-MS 390.2 [M + H]⁺, 801.2 [2M + Na]⁺ as white solids which were contaminated with approximately 5% of (3*aR*, 6*aS*)-[(1*S*)-1-(4-benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]carbamic acid benzyl ester (132) starting material. Each batch was used without further purification (see preparations of (134) and (135) below).

**Preparation of (3*aR*, 6*aS*)-*N*-[(1*S*)-1-(4-benzoyl-6,6-dimethoxy hexa
hydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-*tert*-butyl
benzamide (134)**

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4-Methylmorpholine (0.109 ml, 0.994 mmol) was added to a solution of HBTU (189 mg, 0.497 mmol), 1-hydroxybenzotriazole monohydrate (76 mg, 0.497

-517-

mmol) and 4-(*tert*-butyl)benzoic acid (88 mg, 0.497 mmol) in dimethylformamide (12.5 ml). The solution was stood for 5 minutes then added to (2*S*, 3*aR*, 6*aS*)-2-amino-1-(4-benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrol-1-yl)-4-methylpentan-1-one (133) (prepared as above, 0.497 mmol). The mixture was stirred at ambient temperature for 1 hour 50 minutes then the solvents were removed *in vacuo*. The residue was dissolved in dichloromethane (60 ml) then washed with pH 3 hydrochloric acid (40 ml), saturated aqueous sodium hydrogen carbonate solution (40 ml) and brine (40 ml), then dried (Na₂SO₄) and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 50 : 50 to give (3*aR*, 6*aS*)-*N*-[(1*S*)-1-(4-benzoyl-6,6-dimethoxyhexahydro pyrrolo [3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-*tert*-butyl benzamide (134) as a white solid (230 mg) which contained approximately 5% of (3*aR*, 6*aS*)-[(1*S*)-1-(4-benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl] carbamic acid benzyl ester (132). The latter compound was removed prior to the hydrolysis step (i.e. preparation of EXAMPLE 1 below) by dissolving (220 mg) in methanol (11 ml) then adding to a stirred suspension of 10% palladium on charcoal (70 mg) in ethanol (11 ml) under an atmosphere of argon at 0 °C. The argon was then replaced by hydrogen and the mixture stirred at ambient temperature for 80 minutes, then water (11 ml) was added and the mixture filtered through celite. The filter cake was washed with ethanol (200 ml) then the filtrate concentrated *in vacuo* to give an oily solid (3*aR*, 6*aS*)-*N*-[(1*S*)-1-(4-benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-*tert*-butylbenzamide (134) (203 mg) which was used without further purification. TLC (Single spot, *R_f* = 0.65, EtOAc in heptane 9 : 1), analytical HPLC *R_t* = 21.412 min; HPLC-MS 550.2 [M + H]⁺; Elemental analysis C₃₂H₄₃N₃O₅ req.(*find.*) % C 69.92 (69.52), % H 7.88 (8.12), % N 7.64 (7.40); HRMS C₃₂H₄₄N₃O₅ req. 550.3281, *find.* 550.3284 (0.55ppm).

30 Preparation of (3*aR*, 6*aS*)-*N*-[(1*S*)-1-(4-benzoyl-6,6-dimethoxyhexahydro pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-dimethylaminobenzamide (135)

-518-

4-Methylmorpholine (0.109 ml, 0.994 mmol) was added to a solution of HBTU (189 mg, 0.497 mmol), 1-hydroxybenzotriazole monohydrate (76 mg, 0.497 mmol) and 4-(dimethylamino)benzoic acid (82 mg, 0.497 mmol) in dimethylformamide (12.5 ml). The solution was stood for 5 minutes then added to (2*S*, 3*aR*, 6*aS*)-2-amino-1-(4-benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrol-1-yl)-4-methylpentan-1-one (133) (prepared as above, 0.497 mmol). The mixture was stirred at ambient temperature for 7 hours then the solvents removed *in vacuo* (water bath temperature < 26 °C) to obtain a volume of approximately 3 ml. Stirring was continued for 1.25 hours then the remaining solvent was removed *in vacuo*. The residue was dissolved in dichloromethane (60 ml) then washed with pH 3 hydrochloric acid (40 ml), saturated aqueous sodium hydrogen carbonate solution (40 ml) and brine (40 ml), then dried (Na₂SO₄) and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 65 : 35 to give (3*aR*, 6*aS*)-*N*-[(1*S*)-1-(4-benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-dimethylamino benzamide (135) as a white solid (180 mg, 68%). TLC (Single spot, *R_f* = 0.30, EtOAc : heptane 9 : 1), analytical HPLC *R_t* = 15.789min; HPLC-MS 537.2 [M + H]⁺; Elemental analysis C₃₀H₄₀N₄O₅ .0.4EtOAc req.(*find.*) % C 66.41 (66.60), % H 7.62 (7.92), % N 9.80 (9.51); HRMS C₃₀H₄₀N₄O₅Na req. 559.2896, *find.* 559.2902 (0.95ppm).

Preparation of (3*aR*, 6*aS*)-*N*-[(1*S*)-1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-*tert*-butylbenzamide (EXAMPLE 1).

(3*aR*, 6*aS*)-*N*-[(1*S*)-1-(4-Benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methyl butyl]-4-*tert*-butylbenzamide (134) (0.19 g, 0.345 mmol) was dissolved in ice-cooled trifluoroacetic acid / water (95 : 5 v/v, 10 ml) with stirring. The ice-bath was removed and the mixture stirred at ambient temperature for 3.5 hours. The mixture was then reduced *in vacuo* and evaporated from diethyl ether (2x 10 ml) to give a semi-mobile tan gum (0.3 g). Flash chromatography over silica, eluting with ethyl acetate : heptane mixtures gave (3*aR*, 6*aS*)-*N*-[(1*S*)-

-519-

1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-*tert*-butyl benzamide (EXAMPLE 1) (0.042 g, 24%) as a white solid. TLC (R_f = 0.45, EtOAc : heptane 9 : 1), analytical HPLC single broad main peak, R_t = 19.43-21.37 min., HPLC-MS 504.1 $[M + H]^+$; Elemental analysis $C_{30}H_{37}N_3O_4 \cdot 0.5TFA$ req.(*find.*) % C 66.45 (66.04), % H 6.75 (7.19), % N 7.50 (7.24); HRMS $C_{30}H_{37}N_3O_4Na$ req. 526.2682, *find.* 526.2677 (-0.96ppm); d_H (500 MHz, $CDCl_3$) Tentative assignment of peaks due to presence of rotamers 0.95 (3H, d, J = 6.5 Hz, Leu δCH_3), 1.01 (3H, d, J = 6.2 Hz, Leu δCH_3), 1.31 (9H, s, $C(CH_3)_3$), 1.58-1.81 (3H, m, Leu βCH_2 and Leu γCH), 1.85-2.73 (2H, m, $BzNCHCH_2$), 3.55-3.69 (1H, m, $BzNCHCH_2CH_2$), 3.85-5.20 (6H, m, $BzNCHCH_2CH_2$, $BzNCH_2C(=O)CH$ and Leu αCH), 6.70-6.89 (1H, m, NH), 7.40-7.52 (7H, m, COC_6H_5 and $CHCHCC(CH_3)_3$), 7.65-7.76 (2H, m, $CHCHCC(CH_3)_3$); δ_C (500 MHz, $CDCl_3$) 22.06, 23.28 (2x Leu δCH_3), 24.82 (Leu γCH), 31.11, 31.14 ($C(CH_3)_3$), 31.67, 31.86 ($BzNCHCH_2$), 34.89, 34.92 ($C(CH_3)_3$), 42.43 (Leu βCH_2), 46.10 ($BzNCHCH_2CH_2$), 48.93 (Leu αCH), 60.2 ($BzNCH_2$), 61.0 ($BzNCH$ or $BzNCH_2C(=O)CH$), 68.2 ($BzNCH$ or $BzNCH_2C(=O)CH$), 125.41, 125.49, 125.54, 126.91, 126.97, 127.11, 127.46, 128.33, 128.79, 130.84 (CH aromatics), 130.70, 131.16, 135.0 (quaternary aromatics), 155.35 ($CC(CH_3)_3$), 167.07, 170.67, 172.61 (3 x $NC=O$).

20

Preparation of (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-dimethylaminobenzamide (EXAMPLE 14)

25 Water (1.75 ml) was added dropwise to a stirred solution of (3a*R*, 6a*S*)-*N*-[(1*S*)-1-(4-benzoyl-6,6-dimethoxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-dimethylaminobenzamide (135) (175 mg, 0.327 mmol) in trifluoroacetic acid (17.5 ml) at 0 °C over 3 minutes. The solution was then stirred at ambient temperature for 17 hours then the solvents removed *in vacuo* (water bath < 25 °C). The residue was azeotroped with diethyl ether (25 ml) then the residue purified by flash chromatography over silica eluting with ethyl acetate :

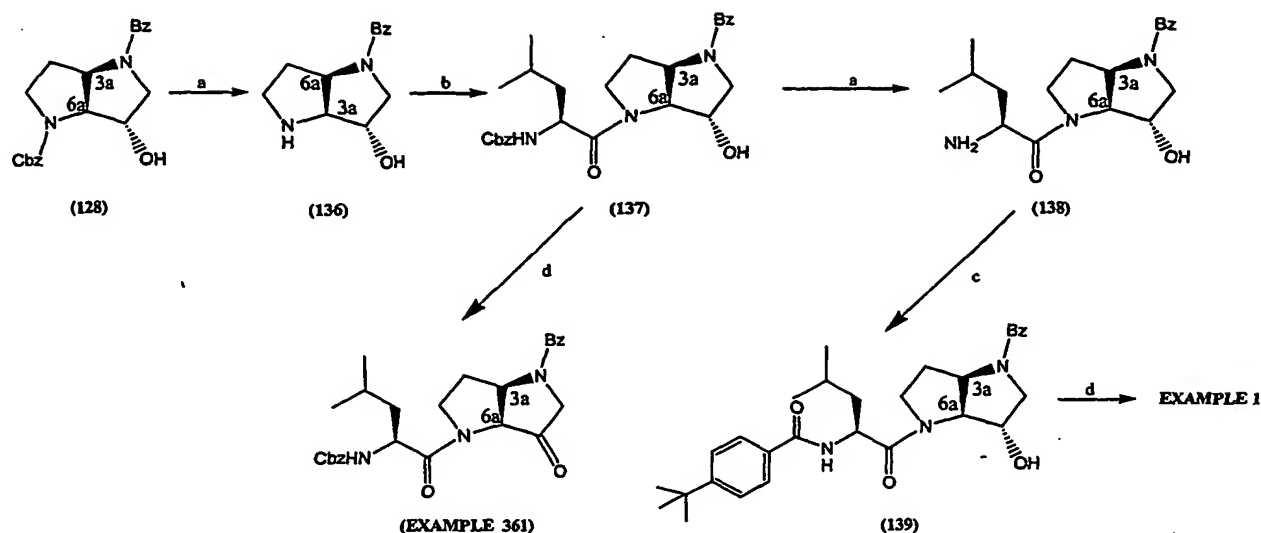
30

-520-

heptane mixtures 0 : 100 to 70 : 30 to give (3aR, 6aS)-N-[(1S)-1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-dimethylaminobenzamide (EXAMPLE 14) as a white solid (113.6 mg, 71%). TLC (Single spot, R_f = 0.25, EtOAc : heptane 9 : 1), analytical HPLC R_t = 14.241min; HPLC-MS 491.2 $[M + H]^+$; $C_{28}H_{34}N_4O_4 \cdot 0.5TFA$ req.(*ind.*) % C 63.64 (63.07), % H 6.35 (6.76), % N 10.23 (9.91); HRMS $C_{28}H_{34}N_4O_4Na$ req. 513.2478, *ind.* 513.2492 (2.72ppm); d_H (500 MHz, $CDCl_3$) Tentative assignment of peaks due to presence of rotamers 0.94 (3H, d, J = 6.5 Hz, Leu δCH_3), 0.99 (3H, d, J = 6.2 Hz, Leu δCH_3), 1.46-1.83 (3H, m, Leu βCH_2 and Leu γCH), 1.90-2.70 (2H, m, BzNCHCH₂), 2.99 (6H, s, N(CH₃)₂), 3.45-3.69 (1H, m, BzNCHCH₂CH₂), 3.90-5.25 (6H, m, BzNCHCH₂CH₂, BzNCH₂C(=O)CH and Leu αCH), 6.58-6.75 (1H, m, NH), 6.60-6.68 (2H, m, CHCN(CH₃)₂), 7.35-7.55 (5H, m, COC₆H₅), 7.60-7.73 (2H, m, CHCHCN(CH₃)₂); δ_C (500 MHz, $CDCl_3$) 22.13, 23.25 (2x Leu δCH_3), 24.78 (Leu γCH), 31.65, 31.85 (BzNCHCH₂), 40.04, 40.09, 40.13 (N(CH₃)₂), 42.35 (Leu βCH_2), 46.12 (BzNCHCH₂CH₂), 48.79 (Leu αCH), 59.99 (BzNCH₂), 60.80 (BzNCH or BzNCH₂C(=O)CH), 67.7 (BzNCH or BzNCH₂C(=O)CH), 110.89, 111.00, 111.04, 111.35 (CHCN(CH₃)₂), 120.17 (CCHCHCN(CH₃)₂), 126.92, 127.12, 127.48, 128.31, 128.63, 128.67, 128.77, 129.00, 130.81, 130.96 (CH aromatics), 135.0 (quaternary aromatics), 152.61 (CN(CH₃)₂), 167.21, 170.69, 173.01 (3 x NC=O).

Alternatively, a useful building block for solution phase synthesis is (3aR, 6S, 6aS)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid benzyl ester (128) described earlier in Scheme 26. The utility of building block (128) is detailed in an alternative synthesis of EXAMPLE 1, through Scheme 27, which is an example of the general synthetic strategy detailed in Scheme 17.

-521-



Scheme 27. (a) Pd-C / H₂, ethanol / methanol. (b) 1eq Cbz-Leu-F, DMF, RT. (c) 1.05eq 4-*tert*-butylbenzoic acid, HBTU, HOBT, NMM, DMF, RT (d) Dess-Martin periodinane, DCM.

5

Preparation of (3*S*, 3*aS*, 6*aR*)-(3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrol-1-yl)phenylmethanone (136).

Ethanol (5 ml) was added cautiously dropwise to 10% palladium on charcoal (50 mg) at 0 °C under an atmosphere of argon over 10 minutes whilst stirring followed by a solution of (3*aR*, 6*S*, 6*aS*)-4-benzoyl-6-hydroxy hexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid benzyl ester (128) (465 mg, 1.27 mmol prepared as above) in ethanol (10 ml). The argon was then replaced by an atmosphere of hydrogen and stirring continued at ambient temperature for 4.5 hours. The hydrogen was then replaced by argon and 10% palladium on charcoal (20 mg) was added at 0 °C. The argon was then replaced with hydrogen and stirring was continued for 4 hours. The hydrogen was replaced by argon then the mixture was filtered through celite. The filter cake was washed with ethanol (75 ml) then the filtrate concentrated *in vacuo* to obtain (3*S*, 3*aS*, 6*aR*)-(3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrol-1-yl)phenylmethanone (136) as a colourless oil (309 mg) which was used without further purification. HPLC-MS 233.1 [M + H]⁺, 465.1 [2M + H]⁺.

-522-

Preparation of (3aR, 6aS)-[(1S)-1-((6S)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-b]pyrrole-1-carbonyl)-3-methylbutyl]carbamic acid benzyl ester (137)

5

Cbz-Leu-F (350 mg, 1.31 mmol) was dissolved in dimethylformamide (5 ml) then added to (3S, 3aS, 6aR)-(3-hydroxyhexahydropyrrolo[3,2-b]pyrrol-1-yl)phenylmethanone (136) (304 mg, 1.24 mmol, prepared as above) under an atmosphere of argon. The solution was stirred for 1.25 hours then the solvents removed *in vacuo*.
10 The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 80 : 20 to give (3aR, 6aS)-[(1S)-1-((6S)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-b]pyrrole-1-carbonyl)-3-methylbutyl]carbamic acid benzyl ester (137) as a white solid (402 mg, 68%). TLC (Single spot, R_f = 0.10, EtOAc : heptane 65 : 35), analytical HPLC R_t = 16.803 min;
15 HPLC-MS 480.2 $[M + H]^+$, 981.3 $[2M + Na]^+$; HRMS $C_{27}H_{33}N_3O_5Na$ req. 502.2318, *found*. 502.2311 (-1.44ppm).

Alternative preparation of (3aR, 6aS)-[(1S)-1-((6S)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-b]pyrrole-1-carbonyl)-3-methylbutyl]carbamic acid benzyl ester (137)

20

Dimethylformamide (1 ml) was added to a mixture of (3S, 3aS, 6aR)-(3-hydroxyhexahydropyrrolo[3,2-b]pyrrol-1-yl)phenylmethanone (136) (24 mg, 0.087 mmol, prepared as above) and Cbz-Leu-OSuc (32 mg, 0.088 mmol) under an atmosphere of argon. The solution was stirred for 20 hours then the solvents removed *in vacuo* to obtain a residue which was dissolved in dichloromethane (20 ml) then washed with water (10 ml), dried (Na_2SO_4) and the solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 30 : 70 to 80 : 20 to give (3aR, 6aS)-[(1S)-1-((6S)-
25 4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-b]pyrrole-1-carbonyl)-3-methylbutyl]carbamic acid benzyl ester (137) as a white solid (25 mg, 60%). TLC (Single spot, R_f = 0.10, EtOAc : heptane 65 : 35), analytical HPLC R_t = 17.301
30

-523-

min; HPLC-MS 480.2 $[M + H]^+$, 981.3 $[2M + Na]^+$; $C_{27}H_{33}N_3O_5 \cdot 0.2EtOAc$ req.(fnd.) % C 67.20 (67.03), % H 7.02 (7.16), % N 8.45 (8.27); d_H (500 MHz, $CDCl_3$) mixture of rotamers, *tentative assignment of proton* 1.2-2.4 (1H, m, 2x Leu δCH_3 , Leu βCH_2 , Leu γCH , BzNCHCH₂), 3.3-4.0 (4H, m, BzNCH₂, CbzLeuNCH₂), 4.2-5.0 (4H, BzNCH, CbzLeuNCH, CHOH, Leu αCH), 5.0-5.1 (2H, OCH₂Ph), 5.4 (1H, d, $J = 8.3Hz$, NH), 7.4-7.6 (10H, aromatic); d_C (125 MHz, $CDCl_3$) 21.73, 21.89 and 23.22, 23.36 (2x Leu $\delta \underline{CH}_3$), 24.59, 24.67 (Leu $\gamma \underline{CH}$), 31.86 (BzNCH \underline{CH}_2), 42.02, 42.22 (Leu $\beta \underline{CH}_2$), 46.52 (CbzLeuN \underline{CH}_2), 50.94, 51.02 (Leu $\alpha \underline{CH}$), 56.58 (BzN \underline{CH}_2), 59.72 (BzN \underline{CH}), 67.00 (O \underline{CH}_2 Ph), 67.98 (CbzLeuN \underline{CH}), 75.25 (\underline{CHOH}), 127.34, 128.02, 128.18, 128.28, 128.36, 128.52, 130.34 (aromatic \underline{CH}), 136.09, 136.18 (aromatic quaternary), 156.18 (NHC=O), 170.08 (PhC=O), 172.32 (CH₂NC=O).

Preparation of (2*S*, 3*aR*, 6*aS*)-2-amino-1-(((6*S*)-4-benzoyl-6-hydroxyhexahydro pyrrolo[3,2-*b*]pyrrol-1-yl)-4-methylpentan-1-one (138)

Ethanol (15 ml) was added cautiously to a stirred mixture of (3*aR*, 6*aS*)-[(1*S*)-1-(((6*S*)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl] carbamic acid benzyl ester (137) (370 mg, 0.77 mmol) and 10% palladium on charcoal (50 mg) at 0 °C under an atmosphere of argon. The argon was replaced by an atmosphere of hydrogen then stirring continued at ambient temperature for 1.75 hours. The hydrogen was replaced by argon then the mixture was cooled to 0 °C before adding a further portion of 10% palladium on charcoal (20 mg). The argon was replaced by hydrogen then stirring continued at ambient temperature for 5.25 hours. The hydrogen was replaced by argon then the mixture was cooled to 0 °C before adding a further portion of 10% palladium on charcoal (20 mg). The argon was replaced by hydrogen then stirring continued at ambient temperature for 14 hours. The hydrogen was replaced by argon then the mixture was cooled to 0 °C before adding a further portion of 10% palladium on charcoal (10 mg). The argon was replaced by hydrogen then stirring continued at ambient temperature for 2 hours. The hydrogen was replaced by argon then the mixture was diluted with ethanol (60 ml) and filtered through celite. The filter cake was

-524-

washed with ethanol (40 ml) then the filtrate concentrated *in vacuo*. The residue was azeotroped with ethyl acetate (35 ml) to obtain (2*S*, 3*aR*, 6*aS*)-2-amino-1-((6*S*)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrol-1-yl)-4-methylpentan-1-one (138) as an oily white solid (270 mg), which was used without further purification. HPLC-MS 346.2 [M + H]⁺, 713.3 [2M + Na]⁺.

Preparation of (3*aR*, 6*aS*)-*N*-[(1*S*)-1-((6*S*)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-*tert*-butyl-benzamide (139)

4-Methylmorpholine (0.17 ml, 1.55 mmol) was added to a solution of HBTU (293 mg, 0.77 mmol), 1-hydroxybenzotriazole monohydrate (118 mg, 0.77 mmol) and 4-(*tert*-butyl)benzoic acid (138 mg, 0.77 mmol) in dimethylformamide (7.5 ml). The solution was stood for 5 minutes then added to (2*S*, 3*aR*, 6*aS*)-2-amino-1-((6*S*)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrol-1-yl)-4-methylpentan-1-one (138) (prepared as above, 0.77 mmol). The mixture was stirred at ambient temperature for 1 hour 5 minutes then the solvents removed *in vacuo* (water bath temperature < 28 °C). The residue was dissolved in dichloromethane (75 ml) then washed with pH 3 hydrochloric acid (60 ml), saturated aqueous sodium hydrogen carbonate solution (60 ml) and brine (60 ml), dried (Na₂SO₄) and the solvents removed *in vacuo*. The residue (512 mg) was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 85 : 15 to give (3*aR*, 6*aS*)-*N*-[(1*S*)-1-((6*S*)-4-benzoyl-6-hydroxyhexahydro-pyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-*tert*-butyl-benzamide (139) as a white solid (263 mg, 68%). TLC (Single spot, *R_f* = 0.15, EtOAc : heptane 9 : 1), analytical HPLC *R_t* = 19.340 min; HPLC-MS 506.2[M + H]⁺; C₃₀H₃₉N₃O₄.0.5EtOAc req.(fnd.) % C 69.97 (69.86), % H 7.89 (7.87), % N 7.65 (7.88); HRMS C₃₀H₃₉N₃O₄Na req. 528.2838, fnd. 528.2818 (-3.89ppm).

Preparation of (3*aR*, 6*aS*)-*N*-[(1*S*)-1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*] pyrrole-1-carbonyl)-3-methylbutyl]-4-*tert*-butylbenzamide (EXAMPLE 1)

-525-

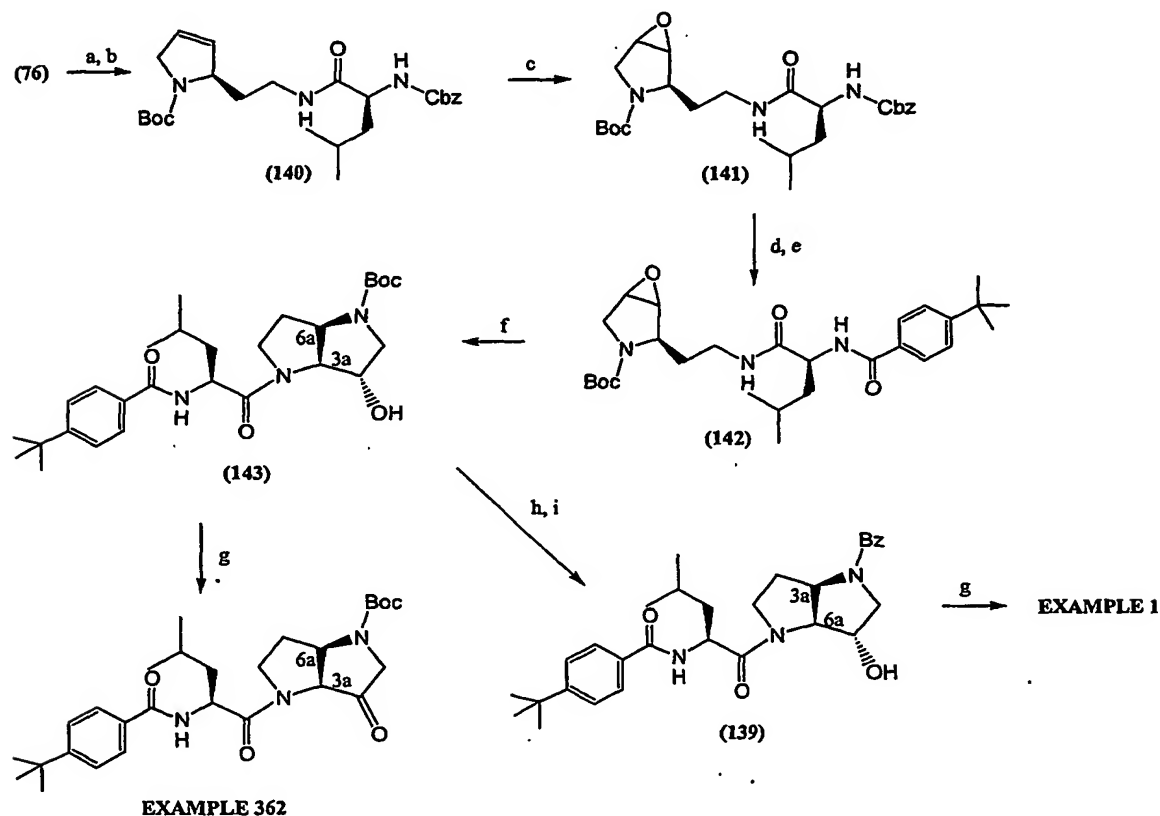
A solution of (3aR, 6aS)-N-[(1S)-1-((6S)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]-4-*tert*-butyl-benzamide (139) (174 mg, 0.345 mmol) in dichloromethane (10 ml) was added to Dess-Martin periodinane (292 mg, 0.689 mmol) under an atmosphere of argon whilst stirring
5 over 2.5 minutes. The mixture was stirred for 3 minutes then trifluoroacetic acid (53 μ l, 0.689 mmol) was added. The mixture was stirred for 14 hours then solvents removed *in vacuo*. The residue was purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures 0 : 100 to 55 : 45 to give (3aR, 6aS)-N-[(1S)-1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-
10 carbonyl)-3-methylbutyl]-4-*tert*-butylbenzamide (EXAMPLE 1) as a white solid (128 mg, 74%). TLC (Single spot, R_f = 0.20, EtOAc : heptane 9 : 1), analytical HPLC broad peak R_t = 19.2-20.6 min; HPLC-MS single broad UV peak, 504.1 [M + H]⁺.

15 **Preparation of (3aR, 6aS)-[(1S)-1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]carbamic acid benzyl ester (EXAMPLE 361)**

A solution of (3aR, 6aS)-[(1S)-1-((6S)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]carbamic acid benzyl ester
20 (137) (15.0 mg, 0.031 mmol) in dichloromethane (0.75 ml) was added dropwise to Dess-Martin periodinane (26.6 mg, 0.063 mmol) under an atmosphere of argon whilst stirring over 1 minute. The solution was stirred for 4.5 hours then purified by flash chromatography over silica eluting with ethyl acetate : heptane mixtures
25 0 : 100 to 80 : 20 to give (3aR, 6aS)-[(1S)-1-(4-benzoyl-6-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carbonyl)-3-methylbutyl]carbamic acid benzyl ester (EXAMPLE 361) as a white solid (8.8 mg, 58%). TLC (Single spot, R_f = 0.35, EtOAc : heptane 9 : 1), analytical HPLC broad peak R_t = 17.7-19.5 min; HPLC-MS single broad UV peak, 478.1 [M + H]⁺, 977.2 [2M + Na]⁺; HRMS
30 C₂₇H₃₁N₃O₅Na req. 500.2161, *find.* 500.2168 (1.26ppm).

-526-

Alternatively, the general synthetic strategy detailed in Scheme 28 involves construction of an extended compound prior to intramolecular ring closure to the 5,5-cis bicycle as the penultimate step. As detailed in Scheme 20, the building block (*R*)-2-(2-azidoethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (76) may be reduced to the primary amine, which in Scheme 28 is directly acylated with a protected aminoacid. Following epoxidation, then conversion of the aminoacid protecting group to a suitable capping group, with all of the potency and specificity components now in place, ring-closure and oxidation provides the final inhibitor compound. The utility of such synthetic flexibility is detailed in an alternative synthesis of EXAMPLE 1, through Scheme 28.



Scheme 28. (a) Ph_3P , H_2O , 1,4-dioxane. (b) 1eq Cbz-Leu-OSu, 2.1eq Na_2CO_3 , 1,4-dioxane, water. (c) *m*-Chloroperoxybenzoic acid, DCM. (d) Pd-C, H_2 , ethanol. (e) 1.05eq 4-*tert*-butylbenzoic acid, HBTU, HOBT, NMM, DMF, RT. (f) 2eq NaH, THF, RT, 16 h. (g) Dess-Martin periodinane, DCM. (h) 4N HCl in 1,4-dioxane, RT, 30mins. (i) Benzoic anhydride, 4-methylmorpholine, DMF, RT, 1hr.

-527-

Preparation of (2R)-2-[2-((2S)-2-benzyloxycarbonylamino-4-methylpentanoylamino)ethyl]-2,5-dihydro pyrrole-1-carboxylic acid *tert*-butyl ester (140)

5 (R)-2-(2-Aminoethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (see preparation of (77) above, ~ 0.63 mmol) was dissolved in 1,4-dioxane (10 ml) with stirring, ice-cooled and a solution of sodium carbonate (0.14 g, 1.32 mmol) in water (10 ml) was added. Cbz-L-Leu-OSu (0.251 g, 0.693 mmol) in 1,4-dioxane (10 ml) was added dropwise over 30 minutes, then the ice bath removed
10 and the mixture stirred for a further 30 minutes. Water (100 ml) was then added and the aqueous phase extracted with dichloromethane (2x 100 ml). The combined organic layers were dried (Na₂SO₄), filtered and reduced *in vacuo* to leave a clear gum (0.54 g). Flash chromatography over silica, eluting with ethyl acetate : heptane mixtures gave (2R)-2-[2-((2S)-2-benzyloxycarbonylamino-4-methylpentanoylamino)ethyl]-2,5-dihydro pyrrole-1-carboxylic acid *tert*-butyl
15 ester (140) (0.21 g, 72%) as a clear oil. TLC (*R_f* = 0.30, EtOAc : heptane 1 : 1), analytical HPLC single main peak, *R_t* = 20.326 min., HPLC-MS 360.1 [M + 2H - Boc]⁺, 404.1 [M + 2H - Bu]⁺, 460.2 [M + H]⁺, 482.1 [M + Na]⁺, 941.2 [2M + Na]⁺; Elemental analysis C₂₅H₃₇N₃O₅ req.(*ind.*) % C 65.34 (65.14), % H 8.11 (8.19), % N 9.14 (9.07); HRMS C₂₅H₃₇N₃O₅Na req. 482.2631, *ind.* 482.2620 (-2.33ppm).

Preparation of (2R)-2-[2-((2S)-2-benzyloxycarbonylamino-4-methylpentanoylamino)ethyl]-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (141)
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(2R)-2-[2-((2S)-2-Benzyloxycarbonylamino-4-methylpentanoylamino)ethyl]-2,5-di hydropyrrole-1-carboxylic acid *tert*-butyl ester (140) (0.20 g, 0.435 mmol) was dissolved in dichloromethane (5 ml) with stirring then *meta*-chloroperoxybenzoic acid (65% reagent, 1.15 g, 4.35 mmol) added. The mixture was stirred at ambient
30 temperature under argon for 16 hours. Dichloromethane (100 ml) was added and the organic phase washed with 10% w/v aqueous sodium hydroxide solution (2x

-528-

100 ml), then dried (Na_2SO_4), filtered and reduced *in vacuo* to leave an oily solid (0.19 g). Flash chromatography over silica, eluting with ethyl acetate : heptane mixtures gave (2*R*)-2-[2-((2*S*)-2-benzyloxycarbonylamino-4-methylpentanoylamino)ethyl]-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (141) (0.19 g, 92%) as an opaque gum. TLC (R_f = 0.35 (major) and 0.42 (minor) (mixture of *anti* and *syn* epoxides), EtOAc : heptane 3 : 1), analytical HPLC single main peak, R_t = 19.21 min., HPLC-MS 376.1 $[\text{M} + 2\text{H} - \text{Boc}]^+$, 420.1 $[\text{M} + 2\text{H} - \text{Bu}]^+$, 476.1 $[\text{M} + \text{H}]^+$, 498.1 $[\text{M} + \text{Na}]^+$, 973.2 $[2\text{M} + \text{Na}]^+$; Elemental analysis $\text{C}_{25}\text{H}_{37}\text{N}_3\text{O}_6$ req.(*find.*) % C 63.14 (63.11), % H 7.84 (7.96), % N 8.84 (8.80); HRMS $\text{C}_{25}\text{H}_{37}\text{N}_3\text{O}_6\text{Na}$ req. 498.2580, *find.* 498.2602 (4.34ppm).

Preparation of (2*R*)-2-{2-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoylamino]ethyl}-6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (142)

15 (i) (2*R*)-2-[2-((2*S*)-2-Benzyloxycarbonylamino-4-methylpentanoylamino)ethyl]-6-oxa-3-azabicyclo [3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (141) (0.17 g, 0.357 mmol) was dissolved in ethanol (5 ml), cooled to 0 °C and 10% palladium on charcoal (0.034 g) added. The mixture was stirred, then evacuated and flushed with hydrogen. The mixture was allowed to warm to ambient temperature, stirred for 45 minutes then filtered through celite. The filter cake was washed with ethanol (3x 10 ml) and the combined organic layers reduced *in vacuo* to provide the crude free amine, which was used without further purification. HPLC-MS 342.2 $[\text{M} + \text{H}]^+$, 683.3 $[2\text{M} + \text{H}]^+$, 705.3 $[2\text{M} + \text{Na}]^+$.

25 (ii) The crude free amine was dissolved in anhydrous dimethylformamide (3 ml) with stirring and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluoro phosphate (HBTU, 0.136 g, 0.357 mmol) and 1-hydroxybenzotriazole monohydrate (HOBT, 0.0548 g, 0.357 mmol) added. 4-Methylmorpholine (78.6 μl , 0.715 mmol) was added and the mixture stirred for 1.5 hours, then reduced *in vacuo*. The residue was dissolved in dichloromethane (50 ml) and washed with pH 3 hydrochloric acid (50 ml), saturated sodium hydrogen carbonate solution (50

-529-

ml) and brine (50 ml). The organic phase was dried (Na_2SO_4), filtered and reduced *in vacuo* to leave a pale yellow gum (0.19 g). Flash chromatography over silica, eluting with ethyl acetate : heptane mixtures gave (2*R*)-2-{2-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoylamino]ethyl}-6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (142) (0.08 g, 45%) as a white crystalline solid. TLC (R_f = 0.26, EtOAc : heptane 3 : 1), analytical HPLC single main peak, R_t = 21.195 min., HPLC-MS 446.2 $[\text{M} + 2\text{H} - \text{Bu}]^+$, 502.3 $[\text{M} + \text{H}]^+$, 524.2 $[\text{M} + \text{Na}]^+$; Elemental analysis $\text{C}_{28}\text{H}_{43}\text{N}_3\text{O}_5$ req.(*find.*) % C 67.04 (67.07), % H 8.64 (8.96), % N 8.38 (7.87); HRMS $\text{C}_{28}\text{H}_{43}\text{N}_3\text{O}_5\text{Na}$ req. 524.3100, *find.* 524.3086 (-2.81ppm).

Preparation of (3*S*, 3*aS*, 6*aR*)-4-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-3-hydroxyhexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (143)

(2*R*)-2-{2-[(2*S*)-2-(4-*tert*-Butylbenzoylamino)-4-methylpentanoylamino]ethyl}-6-oxa -3-aza-bicyclo [3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (142) (0.06 g, 0.12 mmol) was dissolved in tetrahydrofuran (3 ml) with stirring under nitrogen and ice-cooled. Sodium hydride (60% dispersion in oil, 0.010 g, 0.25 mmol) was added over 1 minute and the mixture stirred at ambient temperature for 16 hours. Water (10 ml) was added, then saturated aqueous ammonium chloride solution (5 ml) and the product extracted into ethyl acetate (2x 25 ml). The combined organic layers were dried (Na_2SO_4), filtered and reduced *in vacuo* to leave a clear film (0.06 g). Flash chromatography over silica, eluting with ethyl acetate : heptane mixtures gave (3*S*, 3*aS*, 6*aR*)-4-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-3-hydroxyhexa hydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (143) (0.021 g, 35%) as a white solid. TLC (R_f = 0.40, EtOAc : heptane 2 : 1), HPLC-MS 502.3 $[\text{M} + \text{H}]^+$, 524.2 $[\text{M} + \text{Na}]^+$.

A second product fraction contaminated by starting epoxide (~ 25% by UV analysis) was obtained as a white solid (0.0239 g).

-530-

Preparation of (3a*S*, 6a*R*)-4-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-3-oxo-hexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (EXAMPLE 362)

5 (3*S*, 3a*S*, 6a*R*)-4-[(2*S*)-2-(4-*tert*-Butylbenzoylamino)-4-methylpentanoyl]-3-hydroxy hexahydropyrrolo[3,2-*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (143) (0.021 g, 0.042 mmol) was dissolved in dichloromethane (2 ml) with stirring under argon. Dess-Martin periodinane (0.0373 g, 0.088 mmol) was added and the mixture stirred for 16 hours. The mixture was reduced *in vacuo* and the residue

10 purified by flash chromatography over silica, eluting with ethyl acetate : heptane mixtures to give (3a*S*, 6a*R*)-4-[(2*S*)-2-(4-*tert*-butylbenzoylamino)-4-methylpentanoyl]-3-oxo-hexahydro pyrrolo[3,2-*b*]pyrrole-1-carboxylic acid *tert*-butyl ester (EXAMPLE 362) (0.015 g, 71%) as an off-white gum. TLC (R_f = 0.53, EtOAc : heptane 2 : 1), analytical HPLC single broad main peak, R_t = 20.6-22.5

15 min., HPLC-MS 500.1 $[M + H]^+$. HRMS $C_{28}H_{41}N_3O_5Na$ req. 522.2944, *find.* 522.2952 (1.49ppm); δ_H (500 MHz, $CDCl_3$) 0.85-1.03 (7H, m, 2x Leu δCH_3 + Leu γCH), 1.32 (9H, s, $(CH_3)_3CPh$), 1.47 (9H, s, $(CH_3)_3COCO$), 1.6-1.8 (2H, m, Leu βCH_2), 2.03-2.15 / 2.33-2.45 (2H, b, BocNCHCH₂), 3.50-3.60 (1H, m, LeuNCH₂), 3.75-3.82 (1H, m, BocNCH₂), 3.93-4.02 (1H, m, BocNCH₂), 4.02-

20 4.08 (1H, m, LeuNCH₂), 4.58-4.80 (1H, b, BocNCH or LeuNCH), 4.96-4.98 (1H, b, BocNCH or LeuNCH), 5.0-5.06 / 5.25-5.30 (1H, bm, Leu αCH), 6.83-6.93 (1H, b, LeuNH), 7.42-7.45 (2H, d, J = 8.5 Hz, $(CH_3)_3C-C-CH=CH$), 7.72-7.75 (2H, d, J = 8.5 Hz, $(CH_3)_3C-C-CH=CH$); δ_C (125 MHz, $CDCl_3$) 22.27, 23.48 (2x Leu δCH_3), 24.78 (Leu γCH), 28.32 ($(CH_3)_3COCO$), 29.64, 31.82 (BocNCHCH₂),

25 31.09 ($(CH_3)_3CPh$), 34.88 ($(CH_3)_3CPh$), 42.50 (Leu βCH_2), 45.95 (LeuNCH₂), 49.09, 49.67 (Leu αCH), 52.37 (BocNCH₂), 56.82 (BocNCH), 62.92 (LeuNCH), 81.16 ($(CH_3)_3COCO$), 125.34, 125.44 ($(CH_3)_3C-C-CH=CH$), 126.89, 126.95 ($(CH_3)_3C-C-CH=CH$), 130.83 (quaternary aromatics), 155.26 ($(CH_3)_3COCO$), 167.01 ($(CH_3)_3CPhCO$), 172.28 (Leu $C=O$).

-531-

Preparation of (3aR, 6aS)-N-[(1S)-1-((6S)-4-benzoyl-6-hydroxyhexahydro pyrrolo[3,2-b]pyrrole-1-carbonyl)-3-methylbutyl]-4-tert-butylbenzamide (139)

(i) (3S, 3aS, 6aR)-4-[(2S)-2-(4-tert-Butylbenzoylamino)-4-methylpentanoyl]-3-hydroxyhexahydro pyrrolo[3,2-b]pyrrole-1-carboxylic acid *tert*-butyl ester (143) (0.023 g, 0.046 mmol) was dissolved in 4.0M HCl in 1,4-dioxane (2 ml, 8 mmol) with stirring. After 45 minutes the solvents were removed *in vacuo* and the residue triturated then evaporated from diethyl ether (3x 3 ml) to leave (3aR, 6aS)-4-*tert*-butyl-N-[(1S)-1-((6S)-6-hydroxyhexahydropyrrolo[3,2-b]pyrrole-1-carbonyl)-3-methylbutyl]benzamide hydrochloride as a white solid which was used without further purification; HPLC-MS 402.2 [M + H]⁺, 424.2 [M + Na]⁺, 803.4 [2M + H]⁺, 825.4 [2M + Na]⁺.

(ii) (3aR, 6aS)-4-*tert*-Butyl-N-[(1S)-1-((6S)-6-hydroxyhexahydropyrrolo[3,2-b]pyrrole-1-carbonyl)-3-methylbutyl]benzamide hydrochloride (prepared as above, ~0.048 mmol) was dissolved in dimethylformamide (2 ml) with stirring, then benzoic anhydride (0.0114g, 0.05 mmol) added followed by 4-methylmorpholine (11.1µl, 0.0102 g, 0.101 mmol). After 1 hour, ethyl acetate (25 ml) was added and the organics washed with saturated aqueous sodium hydrogen carbonate solution (25 ml) solution, pH 3 hydrochloric acid (25 ml), and brine (25 ml). The organics were dried (Na₂SO₄), filtered and reduced *in vacuo* to a colourless film (3aR, 6aS)-N-[(1S)-1-((6S)-4-benzoyl-6-hydroxyhexahydropyrrolo[3,2-b]pyrrole-1-carbonyl)-3-methylbutyl]-4-*tert*-butylbenzamide (139) (0.028 g). TLC (*R_f* = 0.16, EtOAc : heptane 4 : 1), analytical HPLC single broad main peak, *R_t* = 19.15 min., HPLC-MS 506.2 [M + H]⁺, 528.2 [M + Na]⁺.

Oxidation to EXAMPLE 1 is as detailed in Scheme 27.

30 EXAMPLE A. Assays for Cysteine Protease Activity

The compounds of this invention may be tested in one of a number of literature based biochemical assays that are designed to elucidate the characteristics of

-532-

compound inhibition. The data from these types of assays enables compound potency and the rates of reaction to be measured and quantified. This information, either alone or in combination with other information, would allow the amount of compound required to produce a given pharmacological effect to be determined.

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General materials and methods

Unless otherwise stated, all general chemicals and biochemicals were purchased from either the Sigma Chemical Company, Poole, Dorset, U.K. or from Fisher Scientific UK, Loughborough, Leicestershire, U.K. Absorbance assays were carried out in flat-bottomed 96-well plates (Spectra; Greiner Bio-One Ltd., Stonehouse, Gloucestershire, U.K.) using a SpectraMax PLUS384 plate reader (Molecular Devices, Crawley, U.K.). Fluorescence high throughput assays were carried out in either 384-well microtitre plates (Corning Costar 3705 plates, Fisher Scientific) or 96-well 'U' bottomed Microfluor W1 microtitre plates (Thermo Labsystems, Ashford, Middlesex, U.K.). Fluorescence assays were monitored using a SpectraMax Gemini fluorescence plate reader (Molecular Devices). For substrates employing either a 7-amino-4-methylcoumarin (AMC) or a 7-amino-4-trifluoromethylcoumarin (AFC) fluorophore, assays were monitored at an excitation wavelength of 365 nm and an emission wavelength of 450 nm and the fluorescence plate reader calibrated with AMC. For substrates employing a 3-amino-benzoyl (Abz) fluorophore, assays were monitored at an excitation wavelength of 310 nm and an emission wavelength of 445 nm; the fluorescence plate reader calibrated with 3-amino-benzamide (Fluka). Unless otherwise indicated, all the peptidase substrates were purchased from Bachem UK, St. Helens, Merseyside, UK. Substrates utilizing fluorescence resonance energy transfer methodology (*i.e.* FRET-based substrates) were synthesized at Incenta Limited using published methods (Atherton & Sheppard, *Solid Phase Peptide Synthesis*, IRL Press, Oxford, U.K., 1989) and employed Abz (2-aminobenzoyl) as the fluorescence donor and 3-nitro-tyrosine [Tyr(NO₂)] as the fluorescence quencher (Meldal, M. and Breddam, K., *Anal. Biochem.*, 195, 141-147, 1991). Hydroxyethylpiperazine ethanesulfonate (HEPES), tris-hydroxymethyl

-533-

aminomethane (tris) base, bis-tris-propane and all the biological detergents (e.g. CHAPS, zwittergents, etc.) were purchased from CN Biosciences UK, Beeston, Nottinghamshire, U.K. Glycerol was purchased from Amersham Pharmacia Biotech, Little Chalfont, Buckinghamshire, U.K. Stock solutions of substrate or inhibitor were made up to 10 mM in 100 % dimethylsulfoxide (DMSO) (Rathburns, Glasgow, U.K.) and diluted as appropriately required. In all cases the DMSO concentration in the assays was maintained at less than 1% (vol./vol.).

Assay protocols were based on literature precedent (Table 4; Barrett, A.J., Rawlings, N.D. and Woessner, J.F., 1998, *Handbook of Proteolytic Enzymes*, Academic Press, London and references therein) and modified as required to suit local assay protocols. Enzyme was added as required to initiate the reaction and the activity, as judged by the change in fluorescence upon conversion of substrate to product, was monitored over time. All assays were carried out at $25 \pm 1^\circ\text{C}$.

Table 4. *The enzyme assays described herein were carried out according to literature precedents.*

Enzyme	Buffer	Substrate	Reference
Cathepsin B	I	Z-Phe-Arg-AMC	a, b
Cathepsin H	II	Bz-Phe-Val-Arg-AMC	a, b
Cathepsin L	I	Ac-Phe-Arg-AMC	b, c
Cathepsin S	I	Boc-Val-Leu-Lys-AMC	c, d
Caspase 1	III	Ac-Leu-Glu-His-Asp-AMC	e
Caspase 2	III	Z-Val-Asp-Val-Ala-Asp-AFC	f
Caspase 3	III	Ac-Asp-Glu-Val-Asp-AMC	g, h
Caspase 4	III	Suc-Tyr-Val-Ala-Asp-AMC	f
Caspase 5	III	Ac-Leu-Glu-His-Asp-AMC	
Caspase 6	III	Ac-Val-Glu-Ile-Asp-AMC	i, j, k
Caspase 7	III	Ac-Asp-Glu-Val-Asp-AMC	
Caspase 8	III	Ac-Ile-Glu-Thr-Asp-AMC	l
Caspase 9	III	Ac-Leu-Glu-His-Asp-AMC	

-534-

Caspase 10	III	Ac-Ile-Glu-Thr-Asp-AMC	
Cruzipain	IV	D-Val-Leu-Lys-AMC	m, n
CPB2.8ΔCTE	XI	Pro-Phe-Arg-AMC	q
<i>S. Aureus</i> Extracellular cysteine peptidase	I	Abz-Ile-Ala-Ala-Pro- Tyr(NO ₂)-Glu-NH ₂	o
Clostripain		Z-Gly-Gly-Arg-AMC	p
FMDV LP	V	Abz-Arg-Lys-Leu-Lys-Gly- Ala-Gly-Ser-Tyr(NO ₂)-Glu- NH ₂	r
Trypsin	VI	Z-Gly-Gly-Arg-AMC	s
Calpain μ	VII	Abz-Ala-Asn-Leu-Gly-Arg-Pro- Ala-Leu-Tyr(NO ₂)-Asp-NH ₂	t
Calpain m	VIII	Abz-Lys-Leu-Cys(Bzl)-Phe-Ser- Lys-Gln-Tyr(NO ₂)-Asp-NH ₂	t
Cathepsin K	IX	Z-Phe-Arg-AMC	u
Cathepsin X	X		v, w

- I: 10 mM BTP, pH 6.5 containing 1 mM EDTA, 5 mM 2-mercaptoethanol and 1 mM CaCl₂
- II: 10 mM BTP, pH 6.5 containing 1 mM EDTA, 142 mM NaCl, 1 mM DTT, 1 mM CaCl₂, 0.035 mM Zwittergent 3-16
- III: 50mM HEPES pH 7.2, 10% Glycerol, 0.1% CHAPS, 142 mM NaCl, 1 mM EDTA, 5 mM DTT
- IV: 100 mM sodium phosphate, pH 6.75 containing 1 mM EDTA and 10 mM L-cysteine
- V: 50 mM tris·acetate, pH 8.4 containing 1 mM EDTA, 10 mM L-cysteine and 0.25% (w/v) CHAPS
- VI: 10 mM HEPES, pH 8.0 containing 5 mM CaCl₂
- VII: 10 mM HEPES, pH 7.5 containing 2 mM 2-mercaptoethanol and 100 μM CaCl₂

-535-

VIII: 10 mM HEPES, pH 7.5 containing 2 mM 2-mercaptoethanol and 200 μ M CaCl_2

IX: 100 mM sodium acetate; pH 5.5 containing 10 mM L-cysteine and 1 mM EDTA

5 X: 100 mM sodium acetate; pH 5.5 containing 10 mM L-cysteine; 0.05% (w/v) Brij 35 and 1 mM EDTA

XI: 100 mM sodium acetate; pH 5.5 containing 10 mM L-cysteine; 142 mM sodium chloride and 1 mM EDTA

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-536-

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Trypanosoma cruzi cruzipain peptidase activity assays

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Wild-type cruzipain, derived from *Trypanosoma cruzi* Dm28 epimastigotes, was obtained from Dr. Julio Scharfstein (Instituto de Biofisica Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil). Activity assays were carried out in 100 mM sodium phosphate, pH 6.75 containing 1 mM EDTA and 10 mM L-cysteine using 2.5 nM enzyme. Ac-Phe-Arg-AMC ($K_M^{app} \sim 12 \mu M$) and D-Val-Leu-Lys-AMC ($K_M^{app} \sim 4 \mu M$) were used as the substrates. Routinely, Ac-FR-AMC was used at a concentration equivalent to K_M^{app} and D-Val-Leu-Lys-AMC was used at a concentration of 25 μM . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

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Leishmania mexicana cysteine protease B (CPB) peptidase activity assays

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Wild-type recombinant CPB without the C-terminal extension (*i.e.* CPB2.8 Δ CTE; Sanderson, S.J., *et al.*, *Biochem. J.*, 347, 383-388, 2000) was obtained from Dr. Jeremy Mottram (Wellcome Centre for Molecular Parasitology, The Anderson College, University of Glasgow, Glasgow, U.K.). Activity assays were carried out in 100 mM sodium acetate; pH 5.5 containing 1 mM EDTA; 200 mM NaCl and 10 mM DTT (Alves, L.C., *et al.*, *Mol. Biochem. Parasitol.*, 116, 1-9, 2001) using 0.25 nM enzyme. Pro-Phe-Arg-AMC ($K_M^{app} \sim 38 \mu M$) was used as the substrate at a concentration equivalent to K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

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-537-

Cathepsin peptidase activity assays

5 Bovine cathepsin S, human cathepsin L, human cathepsin H and human cathepsin B were obtained from CN Biosciences. Recombinant human cathepsin S, human cathepsin K and human cathepsin X were obtained from Dr. Boris Turk (Josef Stefan Institute, Ljubljana, Slovenia). Unless otherwise stated, all peptidase activity assays were carried out in 10 mM bis-tris-propane (BTP), pH 6.5 containing 1 mM EDTA, 5 mM 2-mercaptoethanol and 1 mM CaCl_2 . Human cathepsin H activity assays were carried out in 10 mM BTP pH 6.5, 142 mM NaCl_2 , 1 mM CaCl_2 , 1 mM EDTA, 1 mM DTT, 0.035 mM Zwittergent 3-16. Human cathepsin K assays were carried out in 100 mM sodium acetate; pH 5.5 containing 20 mM L-cysteine and 1 mM EDTA (Bossard, M.J., *et al.*, *J. Biol. Chem.*, **271**, 12517-12524, 1996). Human cathepsin X assays were carried out in 15 100 mM sodium acetate; pH 5.5 containing 20 mM L-cysteine; 0.05% (w/v) Brij 35 and 1 mM EDTA (Santamaria, I., *et al.*, *J. Biol. Chem.*, **273**, 16816-16823, 1998; Klemencic, J, *et al.*, *Eur. J. Biochem.*, **267**, 5404-5412, 2000). The final enzyme concentrations used in the assays were 0.5 nM bovine cathepsin S, 1 nM cathepsin L, 0.1 nM cathepsin B, 0.25nM Cathepsin K; 1 nM cathepsin X and 10 20 nM cathepsin H. For the inhibition assays, the substrates used for cathepsin S, cathepsin L, cathepsin B, cathepsin K and cathepsin H were boc-Val-Leu-Lys-AMC ($K_M^{\text{app}} \sim 30 \mu\text{M}$), Ac-Phe-Arg-AMC ($K_M^{\text{app}} \sim 20 \mu\text{M}$), Z-Phe-Arg-AMC ($K_M^{\text{app}} \sim 40 \mu\text{M}$), Z-Leu-Arg-AMC ($K_M^{\text{app}} \sim 2\mu\text{M}$); Bz-Phe-Val-Arg-AMC ($K_M^{\text{app}} \sim 150 \mu\text{M}$) respectively. In each case the substrate concentration used in each 25 assay was equivalent to the K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

Trypsin peptidase activity assays

30 Human pancreatic trypsin (iodination grade; CN Biosciences) activity assays were carried out in 10 mM HEPES, pH 8.0 containing 5 mM CaCl_2 using 0.1 nM trypsin. For the inhibition assays, Z-Gly-Gly-Arg-AMC ($K_M^{\text{app}} \sim 84 \mu\text{M}$) was

-538-

used as the substrate at a concentration equivalent to K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

5 Clostripain peptidase activity assays

Clostripain (Sigma) activity assays were carried out in 10 mM BTP, pH 6.5 containing 1 mM EDTA, 5 mM 2-mercaptoethanol and 1mM CaCl_2 using 0.3 nM enzyme. For the inhibition assays, Z-Gly-Gly-Arg-AMC ($K_M^{app} \sim 100 \mu\text{M}$) was
10 used as the substrate at a concentration equivalent to K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

Calpain peptidase activity assays

15 Calpain (human erythrocyte μ -calpain and porcine kidney m-calpain; CN Biosciences) activity assays were carried out in 10 mM HEPES, pH 7.5 containing 2 mM 2-mercaptoethanol and CaCl_2 using 25 nM of either enzyme (Sasaki, *et. al.*, *J. Biol. Chem.*, **259**, 12489-12494, 1984). For μ -calpain inhibition
20 assays, the buffer contained 100 μM CaCl_2 and Abz-Ala-Asn-Leu-Gly-Arg-Pro-Ala-Leu-Tyr(NO_2)-Asp- NH_2 ($K_M^{app} \sim 20 \mu\text{M}$; Incenta Limited) was used as the substrate. For m-calpain inhibition assays, the assay buffer contained 200 μM CaCl_2 and Abz-Lys-Leu-Cys(Bzl)-Phe-Ser-Lys-Gln-Tyr(NO_2)-Asp- NH_2 ($K_M^{app} \sim 22 \mu\text{M}$; Incenta Limited) was used as the substrate. In both cases the substrate
25 concentration employed in the assays was equivalent to the K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

30 Extracellular *S. aureus* V8 cysteine peptidase (staphylopain) peptidase activity assays

S. aureus V8 was obtained from Prof. S. Arvidson, Karolinska Institute, Stockholm, Sweden. Extracellular *S. aureus* V8 cysteine peptidase (staphylopain)

-539-

activity assays were carried out using partially purified *S. aureus* V8 culture supernatant (obtained from Dr. Peter Lambert, Aston University, Birmingham, U.K.). Activity assays were carried out in 10 mM BTP, pH 6.5 containing 1 mM EDTA, 5 mM 2-mercaptoethanol and 1mM CaCl₂ using two-times diluted partially purified extract. For the inhibition assays, Abz-Ile-Ala-Ala-Pro-Tyr(NO₂)-Glu-NH₂ ($K_M^{app} \sim 117 \mu\text{M}$; Incenta Limited) was used as the substrate at a concentration equivalent to K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

Foot-and-mouth disease leader peptidase (FMDV-LP) activity assays

Recombinant wild-type FMDV-LP was obtained from Dr. Tim Skern (Institut für Medizinische Biochemie, Abteilung für Biochemie, Universität Wien, Wien, Austria). Activity assays were carried out in 50 mM tris-acetate, pH 8.4 containing 1 mM EDTA, 10 mM L-cysteine and 0.25% (w/v) CHAPS using 10 nM enzyme. For the inhibition assays, Abz-Arg-Lys-Leu-Lys-Gly-Ala-Gly-Ser-Tyr(NO₂)-Glu-NH₂ ($K_M^{app} \sim 51 \mu\text{M}$, Incenta Limited) was used as the substrate at a concentration equivalent to K_M^{app} . The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

Caspase peptidase activity assays

Caspases 1-10 were obtained from CN Biosciences or BioVision Inc. (Mountain View, CA, USA) and all assays were carried out in 50mM HEPES; pH 7.2, 10% (v/v) glycerol, 0.1% (w/v) CHAPS, 142 mM NaCl, 1 mM EDTA, 5 mM dithiothreitol (DTT) using 0.1-1 U per assay. For caspase 1, Ac-Leu-Glu-His-Asp-AMC was used as the substrate; for caspase 2, Z-Val-Asp-Val-Ala-Asp-AFC was used as the substrate; for caspase 3, Ac-Asp-Glu-Val-Asp-AMC was used as the substrate; for caspase 4, Suc-Tyr-Val-Ala-Asp-AMC was used as the substrate; for caspase 5, Ac-Leu-Glu-His-Asp-AMC was used as the substrate; for caspase 6, Ac-Val-Glu-Ile-Asp-AMC was used as the substrate; for caspase 7, Ac-

-540-

Asp-Glu-Val-Asp-AMC was used as the substrate; for caspase 8, Ac-Ile-Glu-Thr-Asp-AMC was used as the substrate; for caspase 9, Ac-Leu-Glu-His-Asp-AMC was used as the substrate; for caspase 10, Ac-Ile-Glu-Thr-Asp-AMC was used as the substrate (Nicholson, D.W. and Thornberry, N.A., *TIBS*, 22, 299-306, 1997; Stennicke, H.R. and Salvesen, G.S., *J. Biol. Chem.*, 272(41), 25719-25723, 1997; Talanian, R.V., *et. al.*, *J. Biol. Chem.*, 272(15), 9677-9682, 1997; Wolf, B.B. and Green, D.R., *J. Biol. Chem.*, 274(29), 20049-20052, 1999). The rate of conversion of substrate to product was derived from the slope of the increase in fluorescence monitored continuously over time.

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Measurement of the apparent macroscopic binding (Michaelis) constants (K_M^{app}) for substrates

The apparent macroscopic binding constant (K_M^{app}) for each substrate was calculated, from the dependence of enzyme activity as a function of substrate concentration. The observed rates were plotted on the ordinate against the related substrate concentration on the abscissa and the data fitted by direct regression analysis (Prism v 3.02; GraphPad, San Diego, USA) using Equation 1 (Cornish-Bowden, A. *Fundamentals of enzyme kinetics* Portland Press; 1995, 93-128.).

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$$v_i = \frac{V_{max}^{app} \cdot [S_o]}{[S_o] + K_M^{app}} \quad (1)$$

In Equation 1 ' v_i ' is the observed initial rate, ' V_{max}^{app} ' is the observed maximum activity at saturating substrate concentration, ' K_M^{app} ' is the apparent macroscopic binding (Michaelis) constant for the substrate, ' $[S_o]$ ' is the initial substrate concentration.

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Measurement of the inhibition constants

The apparent inhibition constant (K_i) for each compound was determined on the basis that inhibition was reversible and occurred by a pure-competitive

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-541-

mechanism. The K_i values were calculated, from the dependence of enzyme activity as a function of inhibitor concentration, by direct regression analysis (Prism v 3.02) using Equation 2 (Cornish-Bowden, A., 1995.).

$$v_i = \frac{V_{\max}^{\text{app}} \cdot [S]}{[S] + \{K_M^{\text{app}} \cdot ([I] / K_i)\}} \quad (2)$$

In Equation 2 ' v_i ' is the observed residual activity, ' V_{\max}^{app} ' is the observed maximum activity (*i.e.* in the absence of inhibitor), ' K_M^{app} ' is the apparent macroscopic binding (Michaelis) constant for the substrate, ' $[S]$ ' is the initial substrate concentration, ' K_i ' is the apparent dissociation constant and ' $[I]$ ' is the inhibitor concentration.

In situations where the apparent dissociation constant (K_i^{app}) approached the enzyme concentrations, the K_i^{app} values were calculated using a quadratic solution in the form described by Equation 3 (Morrison, J.F. *Trends Biochem. Sci.*, 7, 102-105, 1982; Morrison, J.F. *Biochim. Biophys. Acta*, 185, 269-286, 1969; Stone, S.R. and Hofsteenge, J. *Biochemistry*, 25, 4622-4628, 1986).

$$v_i = \frac{F\{E_o - I_o - K_i^{\text{app}} + \sqrt{(E_o - I_o - K_i^{\text{app}})^2 + 4 \cdot K_i^{\text{app}} \cdot E_o}\}}{2} \quad (3)$$

$$K_i^{\text{app}} = K_i (1 + [S_o] / K_M^{\text{app}}) \quad (4)$$

In Equation 3 ' v_i ' is the observed residual activity, ' F ' is the difference between the maximum activity (*i.e.* in the absence of inhibitor) and minimum enzyme activity, ' E_o ' is the total enzyme concentration, ' K_i^{app} ' is the apparent dissociation constant and ' I_o ' is the inhibitor concentration. Curves were fitted by non-linear regression analysis (Prism) using a fixed value for the enzyme concentration. Equation 4 was used to account for the substrate kinetics, where ' K_i ' is the inhibition constant, ' $[S_o]$ ' is the initial substrate concentration and ' K_M^{app} ' is the

-542-

apparent macroscopic binding (Michaelis) constant for the substrate (Morrison, 1982).

The second-order rate of reaction of inhibitor with enzyme

5 Where applicable, the concentration dependence of the observed rate of reaction (k_{obs}) of each compound with enzyme was analysed by determining the rate of enzyme inactivation under pseudo-first order conditions in the presence of substrate (Morrison, J.F., *TIBS*, 102-105, 1982; Tian, W.X. and Tsou, C.L., *Biochemistry*, 21, 1028-1032, 1982; Morrison, J.F. and Walsh, C.T., from Meister (Ed.), *Advances in Enzymol.*, 61, 201-301, 1988; Tsou, C.L., from Meister (Ed.), *Advances in Enzymol.*, 61, 381-436, 1988;). Assays were carried out by addition of various concentrations of inhibitor to assay buffer containing substrate. Assays were initiated by the addition of enzyme to the reaction mixture and the change in
10 fluorescence monitored over time. During the course of the assay less than 10% of the substrate was consumed.

$$F = v_s t + \frac{(v_o - v_s)[1 - e^{-(k_{obs}t)}]}{k_{obs}} + D \quad (5)$$

20 The activity fluorescence progress curves were fitted by non-linear regression analysis (Prism) using Eq. 5 (Morrison, 1969; Morrison, 1982); where 'F' is the fluorescence response, 't' is time, 'v_o' is the initial velocity, 'v_s' is the equilibrium steady-state velocity, 'k_{obs}' is the observed pseudo first-order rate constant and 'D' is the intercept at time zero (i.e. the ordinate displacement of the curve). The
25 second order rate constant was obtained from the slope of the line of a plot of k_{obs} versus the inhibitor concentration (i.e. k_{obs}/[I]). To correct for substrate kinetics, Eq. 6 was used, where '[S_o]' is the initial substrate concentration and 'K_M^{app}' is the apparent macroscopic binding (Michaelis) constant for the substrate.

$$k_{inact} = \frac{k_{obs} \left(1 + [S_o] / K_M^{app} \right)}{[I]} \quad (6)$$

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-543-

Compounds of the invention were tested by the above described assays and observed to exhibit cathepsin K inhibitory activity or inhibitory activity against an alternative CA C1 cysteine protease with an *in vitro* K_i inhibitory constant of less than or equal to 100 μ M. Exemplary inhibition data for examples of the invention are given in Table 5.

Table 5. Exemplary inhibition data (K_i expressed as μ M).

Example N ^o	Human Cathepsin K	Cruzipain	Bovine Cathepsin S	Human Cathepsin L	CPB
2	<0.01	>0.3	>1	>3	>0.2
296	>50	>1	>5	<0.2	>5
250	>5	>5	<0.1	>1	>5
346	>8	<0.2	>10	>3	>5

Human Osteoclast Resorption Assay

Bone resorption was studied using a model where human osteoclast precursor cells were cultured on bovine bone slices for 9 days and allowed to differentiate into bone-resorbing osteoclasts. The formed mature osteoclasts were then allowed to resorb bone. The assay was performed by Pharmatest Services Ltd, Itäinen Pitkakatu 4C, Turku, Finland. After the culture period, bone collagen degradation products were quantified from the culture medium as an index of bone resorption.

-544-

Inhibitor compounds were added into the cell cultures after the differentiation period and their effects on the resorbing activity of mature osteoclasts were determined. The studies included a baseline group without added compounds and a positive control group where a potent cathepsin K inhibitor E-64 was added.

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Human peripheral blood monocytes were suspended to culture medium and allowed to attach to bovine bone slices. The bone slices were transferred into 96-well tissue culture plates containing culture medium with appropriate amounts of important growth factors favouring osteoclast differentiation, including M-CSF, RANK-ligand and TGF- β . The cells were incubated in a CO₂ incubator in humidified atmosphere of 95% air and 5% carbon dioxide at 37°C. At day 7 when osteoclast differentiation was complete, the culture medium was replaced with culture medium containing conditions favouring osteoclast activity. The cell culture was continued for an additional 2 days, during which the formed mature osteoclasts were allowed to resorb bone in the presence of vehicle, control inhibitor (E64) or test compounds. At the end of the culture, bone collagen degradation products released into the culture medium were determined using a commercially available ELISA method (CrossLaps® for culture, Nordic Bioscience, Herlev, Denmark) as an index of bone resorption (see Bagger, Y. Z. et al, J. Bone. Miner. Res. 14 (suppl. 1), S370).

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In this assay, selected EXAMPLES of the invention exhibited more than 70% inhibition of bone resorption at a concentration of 100nM.

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